Dissertation on

"STUDY OF hsCRP LEVELS IN OSTEOARTHRITIS KNEE WITH CLINICAL AND RADIOLOGICAL CORRELATION"

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CERTIFICATE

This is to certify that the dissertation titled "**STUDY OF hsCRP LEVELS IN OSTEOARTHRITIS KNEE WITH CLINICAL AND RADIOLOGICAL CORRELATION"** is the bona fide original work of **Dr.S.SENTHIL KUMAR** in partial fulfilment of the requirement for M.D. Branch - I (General Medicine) Examination of the Tamilnadu DR.M.G.R Medical university to be held in APRIL 2016. The period of study was from April 2015 to September 2015.

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I, **Dr.S.Senthil Kumar** solemnly declare that dissertation titled "**Study Of hsCRP Levels In Osteoarthritis Knee With Clinical And Radiological Correlation"** is a bonafide work done by me at madras medical college and Rajiv Gandhi Government general hospital, Chennai -3 during April 2015 to September. Under the guidance and supervision of my unit chief **Prof.Dr.S.TITO M.D.,** Professor of medicine, Madras medical college and Rajiv Gandhi Government General Hospital, Chennai -3.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical university, towards partial fulfilment of requirement for the award of **M.D. DEGREE IN GENERAL MEDICINE (BRANCH - 1)**

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INTRODUCTION

INTRODUCTION

Osteoarthritis is the most common rheumatologic disease of old age. It is a slowly progressive degenerative disease according for major restriction of activities of daily living in the elderly. Symptoms of osteoarthritis include pain, stiffness and restriction of joint movement and deformity of joint.

Osteoarthritis usually affects knee, hip, hands, Spine rarely ankle. Radiographic evidence of OA outnumbers the clinically evident osteoarthritis.

There is no definite cure for OA. Wide variety treatment measures include weight reduction, modification of activities to reduce stress and load on the joint. Pharmacotherapy, such as analgesics, judicious, use of NSAIDS or intraarticular steroid injection.

Total joint replacement is the treatment of choice but could not be done in all patients.

Although osteoarthritis is a non inflammatory disease, some inflammatory process occurs in the joint causing pain.

Recent investigation focus on various biomarkers to assess osteoarthritis severity and to classify disease progression, the aim of our study is to consider one such marker of inflammation hsCRP as a tool of

disease severity, x-ray grading of knee joint is studied in comparison with hsCRP levels and patient symptoms.

While treating osteoarthritis patient the treating physician should.

- Create an awareness of the disease and educate the patient to change the activities of daily living for secondary prevention of complication.
- To inform the patient about various treatment options available individual risk and benefits of each modality.
- To attain optimal quality of life with appropriate available measures
- To provide adequate rehabilitation measures for selected patients.

Our study design is cross sectional study designed to assess the correlation between severity with its symptoms. X-ray treatment and inflammatory marks. ie hsCRP

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

- To study serum hsCRP levels in sample of osteoarthritic patient.
- To assess hsCRP level in correlation with clinical symptoms and radiological signs.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

Osteoarthritis is chronic degenerative disease of joint, characterised by erosion of articular cartilage, bone hypertrophy at the margins, subchondral sclerosis and varying biochemical and morphological alteration of synovial membrane and joint capsule.

OA is a leading cause of disability, increase in health costs and impaired quality of life.

OA is a disease process affecting entire joint structure including cartilage, synovial membranes, subchondral bone, ligaments and periarticular muscles.

OA is considered as a group of overlapping disorders of varies aetiologies including (genetic) systemic and local factors (biochemical and biomechanical) that ultimately converge to produce a condition with definable morphologic and clinical outcome.

OA may be classified as primary or secondary. Primary OA has no identifiable aetiology or predisposing cause and is the most common type. Secondary OA, has identifiable cause but pathologically indistinguishable from primary OA.Metabolic condition (calcium crystal deposition, hemochromatosis, acromegaly) anatomic factors (leg length

inequality, congenital hip dislocation), traumatic or sequelae of inflammatory disorders ankylosing spondylitis , septic arthritis.

ETIOLOGIES OF SECONDARY OSTEOARTHRITIS

Metabolic
Crystal – associated arthritis
Acromegaly
Ochronosis
Hemochromatosis
Wilson’s diseases
Hyperparathyroidism
Ehlers-Danlos
Gaucher’s diseases
Diabetes
Mechanical/ Local Factors
Slipped capital Femoral epiphysis
Epiphyseal dysplasia
Legg-calve-perthes disease
Congenital dislocation
Femoroacetabular impingement
Congenital hip dysplasia
Limb length inequality

Hypermobility syndromes Avascular necrosis
Traumatic Joint trauma e.g., ACLtear Fracture through joint Prior joint surgery e.g., meniscectomy Charcot joint
Inflammatory Rheumatoid arthritis or other inflammatory arthritis Crystalline arthropathy (gout) History of septic arthritis

EPIDEMIOLOGY

Osteoarthritis is common in women than men. 45% of women over the age of 65 have symptoms of Osteoarthritis, However radiological evidence found in 70% over the age of 65 years.

OA was estimated to the 10^{th} leading cause of non fatal burden in the world in 1990, now it has progressed to 4^{th} leading cause.

PREVALENCE

OA is not reversible hence prevalence of OA increases with the age. Population prevalence shows that Asian females are more prone for OA of the knee but not for the hip. OA of the hip occurs more common in European than Asian Indians.

Prevalence in developing countries is similar to that of developed countries.

The burden will be greater in developing countries like India where life expectancy is improving.

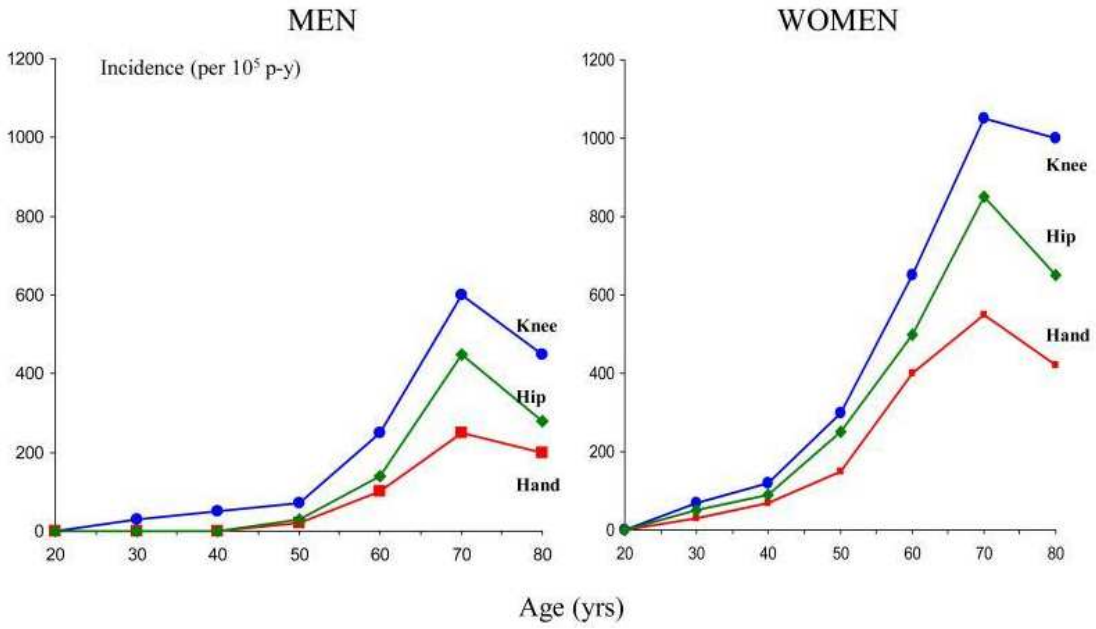
One study shows occupation such as miners, dock workers, jobs involving high knee bending demands and farmers are at increased risk of OA knee.

Farming also increases the risk of OA hip.

OA hip and OA knee are most important from the view of public health based on their prevalence and associated disability.

Mortality: OA is not a life threatening disease but mortality may occur from drugs such as NSAIDS leading to risk of renal failure.

INCIDENCE OF SYMPTOMATIC OSTEOARTHRITIS



ETIOLOGIC FACTORS

AGE:

Most strongly correlated risk factors of OA[1,2] more than 80% of person older than 70 yrs of age.

- OA incidence increases progressively with age at all joints.
- Age related structural change in joint cartilage includes fraying softening and thinning of articular surface and increased apoptosis of chondroctes.
- Radiological changes appear before disease symptoms occur and also progresses as patient age increases [3].

Risk factors for development of osteoarthritis

Risk Factor	Hip OA	Knee OA	Hand OA
Obesity	(+)	+	(+)
Age	+	+	+
Female sex	(+)	+	+
Ethnicity (vs Caucasian)			
Chinese	–	+	–
Genotype	+	+	+
Bone mineral density	+	+	+
Smoking			
Muscle			
Grip Strength			+
Quadriceps Strength		(–)	

JOINT LOCATION

OA is more common in weight bearing hip and knee joints[4], occurs rarely in ankle joint.

OA also occurs in hand joints including thumb interphalangeal joints, spine, shoulders, elbow and ankle are usually not involved.

OBESITY

- Obesity is important risk factor for OA of knee[5,6,7], to some extent also a risk factor for osteoarthritis of hip.
- Obesity increases the force at weight bearing joints.
- Obesity causes change in posture, gait and decrease physical activity contributing to altered joint biomechanics[8].

- Obese patient exhibit varus deformities[9] resulting in increased joint reactive forces in medial compartment, accelerating degenerative process.
- Obesity increases adipose tissue which produces inflammatory leptin, adiponectin. resistin, IL-1,IL-6 and TNF[10,11] which have role in OA.

GENETIC PREDISPOSITION

- OA has higher concordance between monozygotic twins.
- Inherited forms of OA caused by mutation in genes encoding collagen. 2, 4, 5 and 6 as well as cartilage oligomeric matrix protein (COMP[12,13].
- Vitamin D receptor also play a role in bone mineral density, there by genetic abnormalities in vitamin D receptors may cause osteoarthritis.
- IL-1genes are important in coding cartilage formation.
- Chromosome 2q[14] may have the susceptible genes for OA several studies showed.

JOINT MALALIGNMENT AND TRAUMA

- Joint malalignment and trauma causes rapid development of OA.
- May also start slow process resulting in symptomatic OA years later.
- May cause reduced blood supply to the peri articular region.
- Altered joint geometry interferes with nutrition of cartilage or alter load distribution both may cause altered biochemical composition of cartilage[15, 16].
- Joint incongruence such as malreduced intraarticular fractures, developmental dysplasia of hip, recurrent dislocation of patella leads to early OA onset.
- Repetitive high impact sports strongly associated with joint injury and increases risk of OA in lower limb[17].
- Regular exercise maintains good articular structure and metabolic function.
- Articular cartilage is vulnerable to repetitive impact loading[18], excess loads cause micro fractures causing callus formation and remodelling resulting in new bone that is stiffer and acts as less effective shock absorber predisposes to cartilage degeneration.

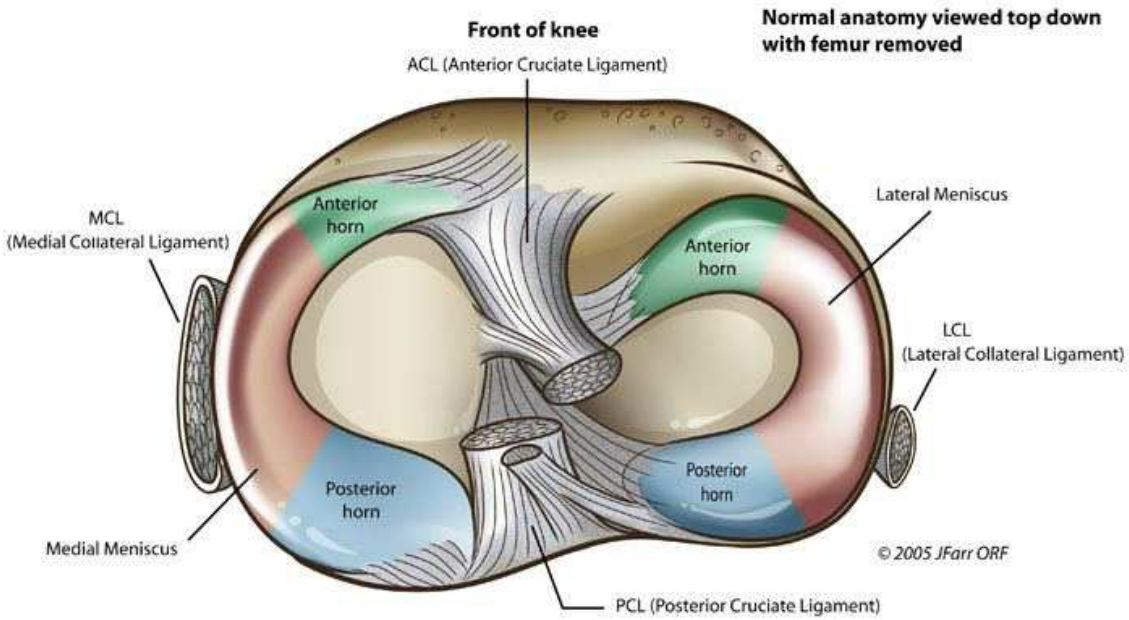
GENDER

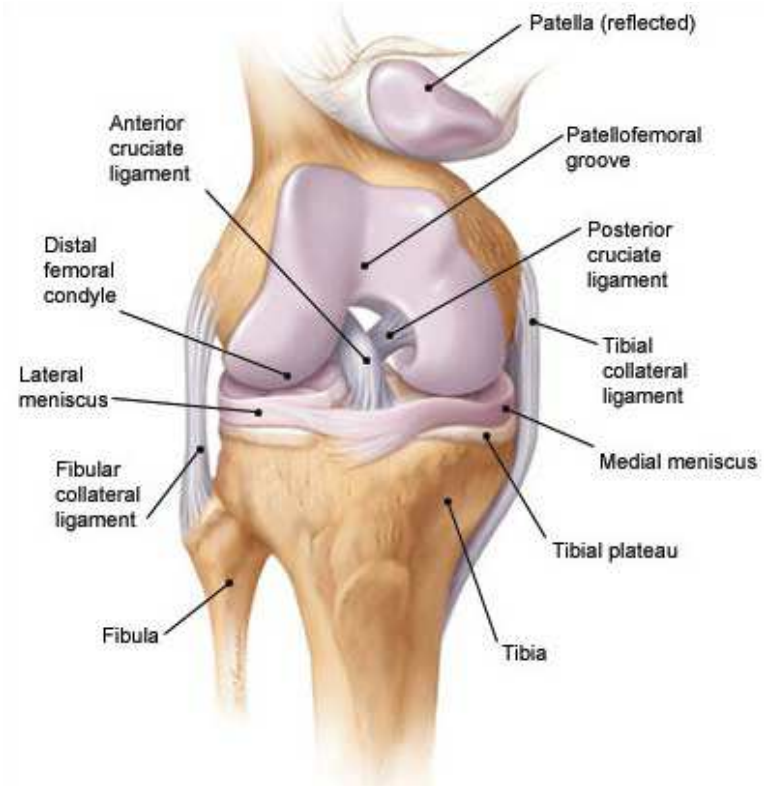
- Women are twice likely at risk of developing OA than men.
- Before the age of 50 years women have lower prevalence of OA than men but after age of 50 years, women have higher prevalence of OA[19], possibly due to oestrogen deficiency.
- Women have many number of joints involved compared to men.
- Oestrogen functional receptors are present in articular chondrocytes[20].
- Oestrogen replacement therapy in postmenopausal women have shown decreased risk of knee and hip OA[21].
- A prospective study showed when incident and progressive radiographic knee OA were combined current ERT users had 60% less risk of knee OA.

CHANGES IN OSTEOARTHRITIS

Before discussing changes in osteoarthritis shortly review of anatomy of knee.

ANATOMY OF THE KNEE





The knee is a complex hinge joint with tibio-femoral and patella-femoral components.

It has synovial capsule that extends under the quadriceps (the suprapatellar pouch) reaching cm above the superior edge of the patella. The joint is largely subcutaneous, allowing easy palpation of the patellar tendon, tibial plateau margin and femoral condyles. The knee depends on its muscular and ligamentous structures for stability..

The hamstring muscles flex the knee. Extension requires the quadriceps muscles, quadriceps tendon patella, patellar tendon and tibial tuberosity. Any disruption of this ‘extensor apparatus’ prevents straight-leg raising or produces an extensor lag (a difference between active and passive ranges of extension).

The medial and lateral collateral ligament resist valgus and varus stress respectively. The anterior cruciate ligament prevents anterior subluxation of the tibia on the femur, and the posterior cruciate ligament resists posterior translation. The media and lateral menisci are crescentic fibrocartilaginous structures that lie between the tibial plateaus and the femoral condyles.

MORPHOLOGIC CHANGES;

Early OA

Articular cartilage surface becomes roughened and irregular, superficial clefts within cartilage appear.

Cartilage surface is fibrillated and small cracks appear matrix swelling , chondrocyte proliferation or limited amount of apoptosis may be evident.

Advanced OA

Articular cartilage surface is more irregular and superficial cleft extend into middle zone of cartilage.

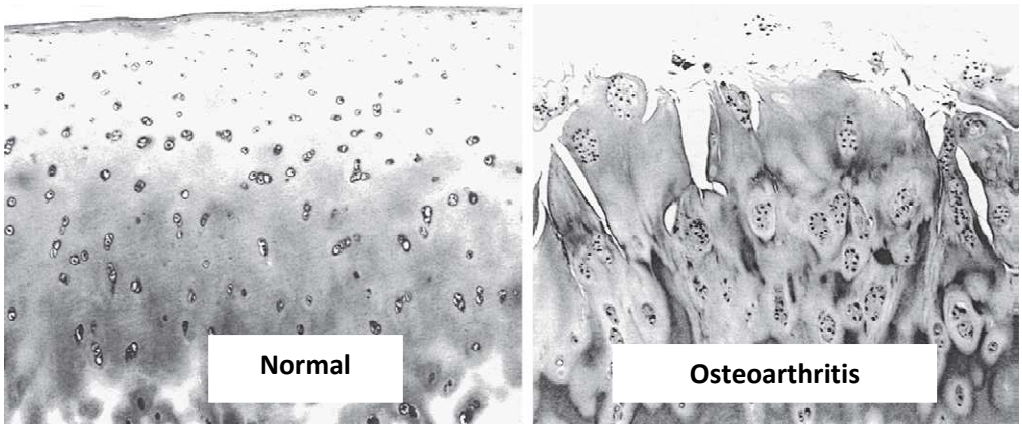
Portion of superficial zone may be missing

Clefts deepens, surface irregularities increase and articular cartilage finally ulcerate and exposes underlying bone.

Joint articulates on exposed bone causes eburnation and bone thickening.

EARLY REPARATIVE, PROLIFERATIVE AND HYPERTROPHIC CHANGES:

- Increase in number of chondrocytes in the form of clones and clusters[22] is an attempt to self repair of damaged cartilage.
- Chondrocytes are quiescent neither committing to proliferation nor to hypertrophic differentiation.
- In early osteoarthritis chondrocytes proliferate and express higher level of matrix protein such as aggre can and type II[23] collagen as well as stem cell markers[24] and markers of hypertrophic changes.
- Chondrocytes contribute to OA pathogenesis and progresses through releasing matrix degrading enzymes, growth factors and inflammation cytokines[25].



Osteoarthritic cartilage has surface irregularities, with clefts and cloning of chondrocytes.

OSTEOPHYTE FORMATION

- Osteophytes are newly formed fibrocartilage and bone formed in periphery margins of joints between cartilage and periosteum.
- Osteophytes are believed to arise by chondrogenic differentiation of progenitor cells commonly from periosteum[26]. Osteophytes can contribute to stability of joints[27]. TGF-BETA[28], BMP'S[29], IGF[30], Fibroblast growth factor are the factors promoting chondrogenic stem cell differentiation.
- Relation between osteophyte formation and repair response is evident by animal models of OA in which osteophyte formation is evident as early as 3 days after injury.
- During OA progression osteophytes limit joint movement and become painful.

HYPOCELLULARITY

- Normal adult cartilage has density between 24000/mm^3 in the surface zone and 8000/mm^3 in the deep zone.
- Ageing cartilage has decreased cell number.
- Cartilage has decreased cell synthesis function.
- Cell death may occur via necrosis or apoptosis[31].

- Inhibition of apoptosis by interfering with caspase activation is being investigated for preventing secondary OA.

ALTERATION IN CARTILAGE MATRIX METABOLISM

BIOCHEMICAL CHANGES

- In early OA, cartilage water content increases causes tissue swelling and altering biomechanical functions.
- In advanced OA, type 1 collagen concentration with in ECM increases, proteoglycan concentration decreases[32], keratam sulphate concentration reduced, ratio of chondroitin -4-sulfate to chondroitin -6-sulfate increases. All is promotes immature cartilage production[33.]
- Calcium crystals are found in cartilage of elderly and crystal arthropathy may coexist with OA[34].
- High levels of pyrophosphate correlates with joint damage.
- Hemosiderin , copper, homogenitisic acid polymers, monosodium urate crystals, calcium pyrophosphate dehydrate are examples of precipitating factors in the development of OA.

METABOLIC CHANGES

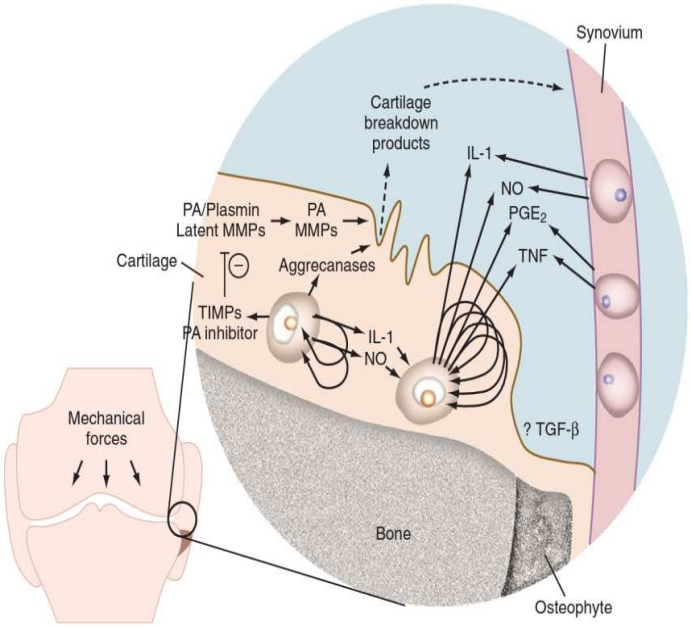
- Early OA activates chondrocytes which produce cartilage of inferior quality.

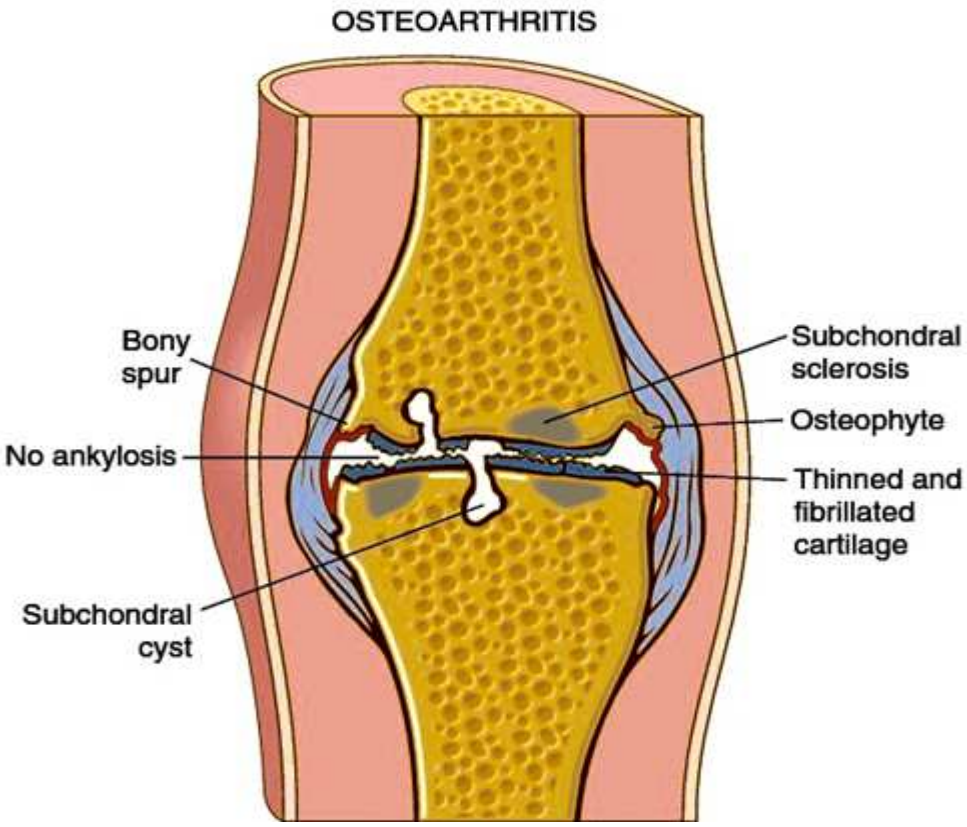
ANABOLIC FACTORS (TRANSFORMING GROWTH FACTOR-B, BONE MORPHOGENETIC PROTEINS) AND CARTILAGE REPAIR.

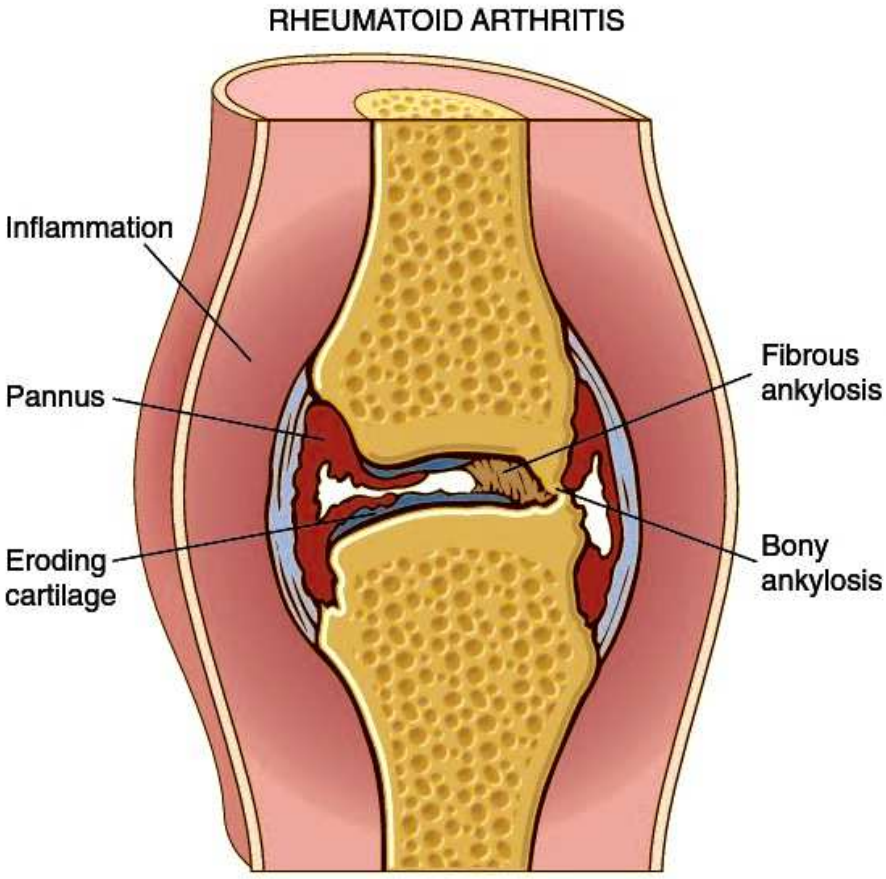
- TGF-beta is essential for formation and maintenance of cartilage.
- TGF-beta functional interference can lead to OA in animal models.
- TGF-beta affects cartilage homeostasis at different levels
- Enhances stem cell chondrogenesis.
- Also increases anticatabolic factors such as TIMPs and PAI-1
- Attenuates the cellular response to inflammatory cytokines IL-1β and TNF.
- BMP's are related to TGF-beta structurally, but activate different receptors and intra cellular signalling molecules function similar to that.
- Impaired BMP signalling affects OA susceptibility particularly BMP protein.
- BMP 7 is found to be decreased in osteoarthritic cartilage and supplementation of BMP 7 can reduce arthritis in animals.

PICTORIAL REPRESENTATION OF

PATHOGENESIS OF OA






RHEUMATOID ARTHRITIS
Inflammation
Pannus
Eroding cartilage
Fibrous ankylosis
Bony ankylosis

CATABOLIC FACTORS AND CARTILAGE DEGRADATION

- IL-1 and TNF stimulate synthesis and secretion of many proteases and MMPs
- MMPs cause proteolysis and cartilage remodelling
- Enzymes stimulated by IL-1 and TNF are collagenase ,stromelysin, gelatinase, aggrecanase and tissue plasminogen activator
- TPA converts plasminogen to plasmin that can activate latent cartilage degrading enzymes.
- Cartilage integrity is maintained by balance between anabolic and catabolic factors

BONE ABNORMALITIES

i. **Osteophyte formation**

- It is bony proliferation at the join margin in the floor of cartilage lesions. These are responsible for pain and restriction of join movement.
- Osteophyte results from penetration of blood vessels into the degenerating cartilage.
- Subchondral bon cyst are created by entry of synovial fluid through defects in cartilage.
- Immobilization and steroids decrease size of Osteophytes.

ii. Subchondral bone sclerosis

- Remodelling and hardening of subchondral bone occurs in osteoarthritis known as subchondral sclerosis.
- It may be evident radiologically before loss of cartilage.

iii. Bone marrow lesion.

- It is detected by MRI are associated with OA.
- May contribute to pain felt by the patient.
- Its presence is predictive of disease progression development of cartilage defects and degradation and the need for joint replacement.

MORPHOLOGICAL CHANGES

1-Subchondral bone sclerosis, 2-Subchondral cyst, 3- Damaged cartilage.

INFLAMMATORY MOLECULES PRODUCED BY ARTICULAR CARTILAGE CYTOKINES AND CHEMOKINES

- Established osteoarthritis has increased inflammatory cytokines.IL-1β and TNF produced by articular chondrocytes
- IL-1 and TNF induce chondrocytes and synovial cells to produce other inflammatory mediators like IL-6 ,IL-8, Nitric oxide and prostaglandin E
- IL-1R antagonist have been studied and shown to retard OA progression in animals[35].

PROTEINASES

Promote cartilage proteolysis through induction of proteases in particular matrix metallo proteinases

Two family of protease (MMPs) are

- Collagenase that breakdown type II collagen MMP (1,8,13,28) and proteoglycans
- Aggrecanase which mediate aggrecan degradation in cartilage[36,37].
- These two are expressed in OA cartilage at the site of lesion suggesting they have a role in ECM degradation.

NITRIC OXIDE

- Produced by Inducible nitric oxide synthase.
- Over production of nitric oxide by chondrocytes in response to cytokines IL-1 and TNF leads to cartilage destruction.
- Cause articular cartilage degradation by inhibition of collagen and proteoglycan synthesis[38].
- And metalloproteinase activation[39].
- Increased susceptibility to injury by other oxidants (H_2O_2)[40].
- Apoptosis[38].

TGF-beta

- TGF beta down regulates proteoglycans MMP1 and MMP13
- TGF beta also acts on IL-1 and TNF-receptors on chondrocytes41.
- TGF beta 2 suppress cleavage of type 11 collagen by collagenases

HYALURONIC ACID

- Hyaluronic acid can be detected in synovial fluid and serum of OA patients.
- Hyaluronic acid is produced by synovium and in OA its production is increased.

- It provides lubrication for joint mobility

PROSTAGLANDINS

- Inducible COX-2 is expressed largely in OA chondrocytes and produce PGE2.
- COX-2 inhibitions by NSAIDS prevents IL-1 mediated proteoglycans degradation

F-SPONDIN

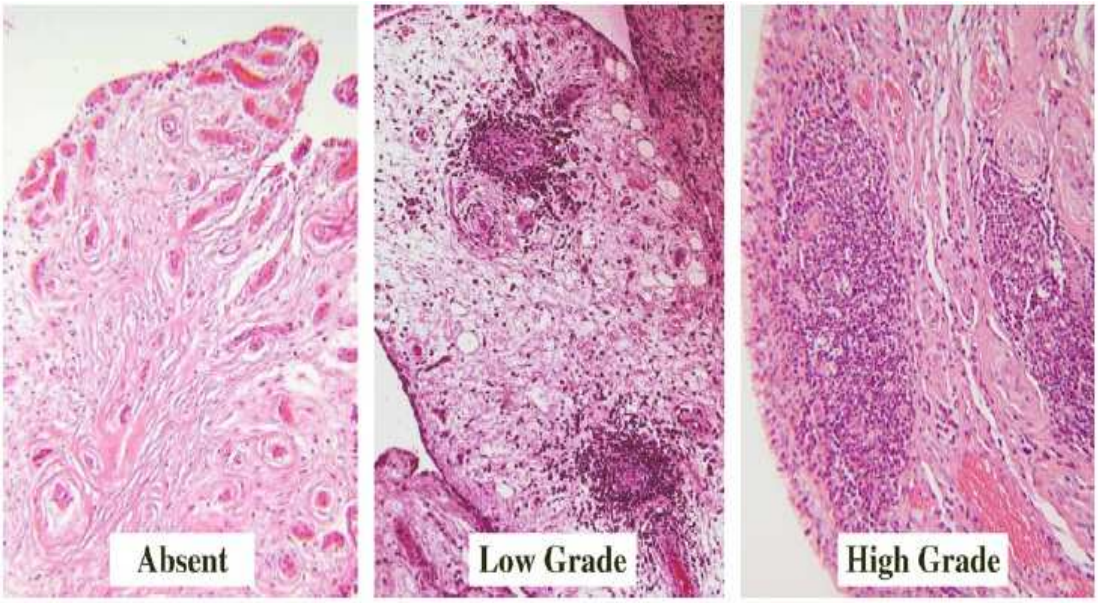
- New mediator in OA cartilage is a neuronal ECM glycoprotein regulating cartilage degradation through TGF-beta and PGE2 pathway

ALTERATION IN SYNOVIAL TISSUE

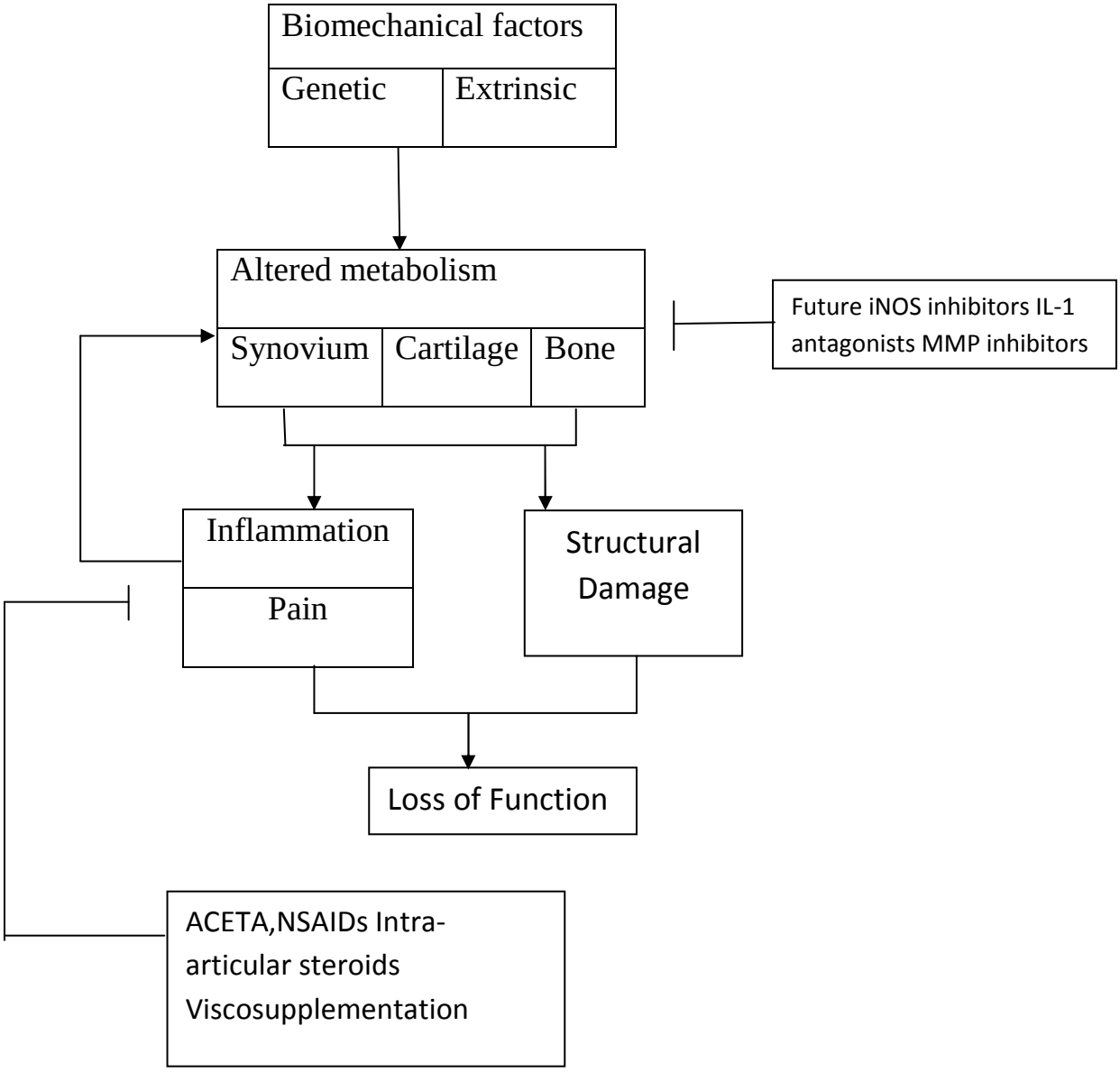
- Synovial inflammation and effusion are key features of OA pathophysiology
- Some degree of synovitis has been observed in early OA.
- Clinical symptoms and signs such as joint swelling and effusion, stiffness, pain reflect synovial inflammation
- Synovial histology shows synovial hypertrophy and hyperplasia
- Synovial inflammation is confined to areas adjacent to pathologically damaged cartilage and bone.

- Activated synovium release proteinase and cytokines destructing cartilage[42].

GRADING OF SYNOVIAL INFLAMMATION



PATHOPHYSIOLOGY OF OA



BIOMARKERS OF OA

COMP, cartilage intermediate layer protein (CILP), cartilage link protein matrilin and minor collagen and hyaluronic acid are synthesized and degraded in OA in excess levels.

- In healthy cartilage this molecules have relatively slow turn over.- These markers of cartilage matrix synthesis and degradation can be used as biomarkers of OA
- Biomarkers of OA can be used to find
    - **B**urden of disease
    - **I**nvestigative markers
    - **P**rognostic markers
    - **E**fficacy and effectiveness of intervention
    - **D**iagnostic

Examples of burden of disease and prognosis includes serum COMP,

SERUM HA, AND URINARY CXT II

- One study of patients with OA knee compared MRI findings with level of serum HA ,osteocalcin , cartilage glycoprotein 39,COMP,and urine c-telopeptide of type collagen. Findings suggested one time measurement of HA or short term increase

in CTX II would identify patient at greater risk for OA progression[44].

CRP

- OA is not considered as inflammatory disease but it definitely involves inflammatory process and it provides promise for biomarkers
- Elevated levels of CRP appear to be predictive of radiographic progression of long term knee OA.
- In a study of 1025 women, higher CRP levels are associated with statistically significant increase in both prevalent and incident OA and greater knee severity
- Bilateral OA knee patient has comparatively higher CRP levels than unilateral OA
- Body mass index should be taken into account for CRP levels[45.]
- CRP are modestly but significantly elevated in OA early knee OA and Predictive of disease progression.

COMP

- COMP is a non-collagenous ECM protein synthesized by cartilage and synovium is abundant in articular cartilage[46,47,48,49].

- COMP levels helpful in assessing presence and progression of OA
- Synovial fluid COMP levels elevated in patients with knee injury ligaments or meniscal injury.
- Serum COMP levels are higher in patients with rapidly progressing joint damage

HYALURONIC ACID

- HA is a cartilage degradation marker and can be detected in serum and synovial fluid[50].
- HA levels reflect activity of synovium , but proteoglycan levels reflect turnover of cartilage.
- Higher serum HA levels have been correlated with number of joints involved and degree of clinical severity.
- Serum HA levels also serve as predictor of OA disease progression.

BIO MARKERS IN OSTEOARTHRITIS

Table 1. Candidate inflammatory prognostic biomarkers in knee osteoarthritis

Inflammatory biomarker subgroup	Candidate biomarkers	Presumed source: C = cartilage, S = synovium, B = bone	Selected recent citations
Cytokine/chemokines, complement and lipid mediators	hsCRP	Liver	[14▪,31▪,32▪▪,33▪▪]
	IL-1β	C,S,B	[34,35,36▪,37▪▪]
	IL-1Ra	C,S,B	[36▪,38▪▪]
	TNF-α	C,S,B	[32▪▪,38▪▪,39,40▪]
	IL-6	C,S,B	[32▪▪,39,40▪,41]
	IL-7	C,S	[42▪]
	IL-15	C,S	[38▪▪,43▪▪]
	15-HETE	C,S	[44]
	PGE2	C,S,B	[36▪,44]
	Complement	C,S	[45▪▪]
Obesity-related inflammatory biomarkers	Leptin	Adipose tissue	[33▪▪,46▪▪]
	Adiponectin	Adipose tissue	[33▪▪,46▪▪]
	Resistin	Adipose tissue	[33▪▪,46▪▪]
Transcriptomic biomarkers	PBL expression of IL-1β / TNFα	PBL	[37▪▪,58▪]

15-HETE, 15-hydroxy eicosatetraenoic acid; hsCRP, highly sensitive C-reactive protein; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; PBL, peripheral blood leukocytes; PGE2, prostaglandin E2; TNF, tumor necrosis factor .

	Biomarkers	Samples	Expression	References
Unique characteristics of CTX-II	CTX-II	Urine	Cartilage, subchondral bone, osteophyte	van Spil *et al.* [2013]
				van Spil *et al.* [2012]
Insight into the pathophysiology of OA revealed by biochemical biomarkers	UA	Joint fluid	Inflammation	Denoble *et al.* [2011]
	n-6 / n-3 PUFAs	Plasma	Synovitis	Baker *et al.* [2012]
	COMP	Serum	Cartilage	Erhart-Hledik *et al.* [2012]
	Adipokines	Serum	Inflammation	van Spil *et al.* [2012]
Candidates for novel biomarkers in OA revealed by proteomics	Hemopexin	Serum	Glycosylation	Fukuda *et al.* [2012]
	Clusterin	Serum		
	AGP-2	Serum		
	MSP	Serum		
	Fib3-1, Fib3-2	Urine	Cartilage	Henrotin *et al.* [2012]

AGP-2, α1 acid glycoprotein-2; COMP, cartilage oligometric matrix protein; CTX-II, C-terminal telopeptides of type II collagen; Fib, fibulin; MSP, macrophage stimulating protein; N-6/N-3 PUFAs, ω6/ω3 polyunsaturated fatty acids; OA, osteoarthritis; UA, uric acid.

CLINICAL FEATURES OF OA

ACR radiologic and clinical criteria for OA

KNEE: CLINICAL

1) Knee pain for most days of prior month
2) Crepitus with active joint motion
3) Morning stiffness lasting < 30 min
4) Bony enlargement of the knee on examination
5) Age ≥ 38 yrs

Diagnosis requires 1+2+4 or 1+2+3+5 or 1+4+5

Knee clinical and Radiographic

1) Knee pain for most days of prior month
2) Osteophytes at joint margin
3) Synovial fluid typical of osteoarthritis
4) Age ≥ 40 yrs
5) Morning stiffness lasting < 30 min
6) Crepitus with active joint motion

Diagnosis requires 1+2+3 or 1+2+4 or 1+3+4

CLINICAL FEATURES:

General symptoms and signs

- OA affects knees, hands, feet, hip and spine.
- OA patients describe pain in joint that is worse with activities with limited morning stiffness <30 minutes.
- Pain and stiffness occurs after rest called **"gelling" phenomenon.**
- Affected joints in OA have bony enlargement and on examination have crepitation

KNEE OA:

- Insidious onset of pain with gelling and limited range of movements.
- OA patient describe pain and limitation with walking transferring as from seated to standing.
- Stiffness, loose bodies and meniscal lesions may contribute to "locking" sensation.
- Pain over medial or lateral joint line may be present on palpation.

Pain Mechanisms in Osteoarthritis

Pain, The main presenting symptom of osteoarthritis, is presumed to arise from a combination of mechanisms, Including the following:

- Osteophytic periosteal elevation
- Vascular congestion of subchondral bone, leading to increased intraosseous pressure
- Synovitis with activation of synovial membrane nociceptors
- Fatigue in muscles that cross the joint
- Overall joint contracture
- joint effusion and stretching of the joint capsule
- torn menisci
- inflammation of periarticular bursae
- periarticular muscle spasm
- psychological factors
- crepitus (a rough or crunchy sensation)
- central pain sensitization

- Effusions when present are usually without signs of inflammation.
- There can be popliteal bursa enlargement. - Baker's cyst.
- Pain over anserine bursa or greater trochanter such in OA due to altered biomechanics.[52]

- Soft tissue symptoms may be responding to steroid injection relieving pain.
- Malalignment, usually varus deformity is seen in severe disease but also seen in mild or early disease
- Varus thrust when clinically appreciated is risk factor for OA disease progression.[53]
- Severe disease may have flexion deformity and joint instability
- Quadriceps weakness is early modifiable risk factor for OA progression especially in women[54,55]; In late stages Quadriceps atrophy can occur
- Alteration in proprioception and vibration sense have been demonstrated
- Patellofemoral OA contribute to pain and disability at knee[56]; pain is during ascending or descending stairs located anteriorly

POLYARTICULAR OSTEOARTHRITIS.

- Long back it has been recognised OA can occur simultaneously in multiple joint sites.[57]
- Polyarticular osteoarthritis also called as general osteoarthritis (GOA).

- Kellgren and Moore gave the first clinical description of GOA, involving heberden's nodes and the CMC joints, with the spine, knees, hips, and feet involved in descending frequency.
- Newer definition for GOA is more than three or five joint sites affected[58] multiple hand joint involvement, nodal hand OA with other joint involvement[59], or summed scores of OA across multiple joints.
- Its important to recognise a patient with single joint involvement is likely to have involvement of other joints.

DIAGNOSTIC TESTING

- Diagnosis of OA is a clinical one, lab testing is rarely required
- Radiographs usually not required
- Purpose of additional tests is primarily to rule out potentially treatable other metabolic and inflammatory arthropathies.

LAB TESTING

- CBC, Blood glucose, serum creatinine, LFT Before initiation of pharmacological therapy
- Rheumatoid factor, thyroid function test may rarely be required

SYNOVIAL FLUID

- Synovial fluid is usually normal or mildly inflammatory. It appears clear and colorless or mild yellow
- Leukocyte count less than or equal to 2000cells per mm3[60]
- Fluid is obtained while giving steroid injection.
- Diagnostic aspiration will be done in cases of effusion.
- Coexisting CPPD crystals can be identified.

MOLECULAR BIOMARKER

- Urinary c telopeptide fragments of type II collagen U CTX II is associated with occurrence and progression of radiographic OA.[61]
- Biomarkers in serum, urine or synovium currently used in research.

IMAGING:

- Conventional radiography is inexpensive and widely available, used to confirm the diagnosis and exclude other conditions.

- X-ray in OA show osteophytes, joint space narrowing, osteosclerosis and subchondral bone cysts.

- Kellgren-lawrence grading system commonly used for research purpose range from 0 (no osteophytes; no joint space narrowing) to 4 (severe joint space narrowing with subchondral sclerosis).

- K-L grade 2 is usually considered diagnosis of OA.

- K-L grading is much less helpful in OA of hip.

- Osteoarthritis Research Society International grading system (OARSI) view osteophytes and joint space narrowing separately and assign separate scores[62].

- Imaging of knees should involve both knee joint and in weight bearing state.

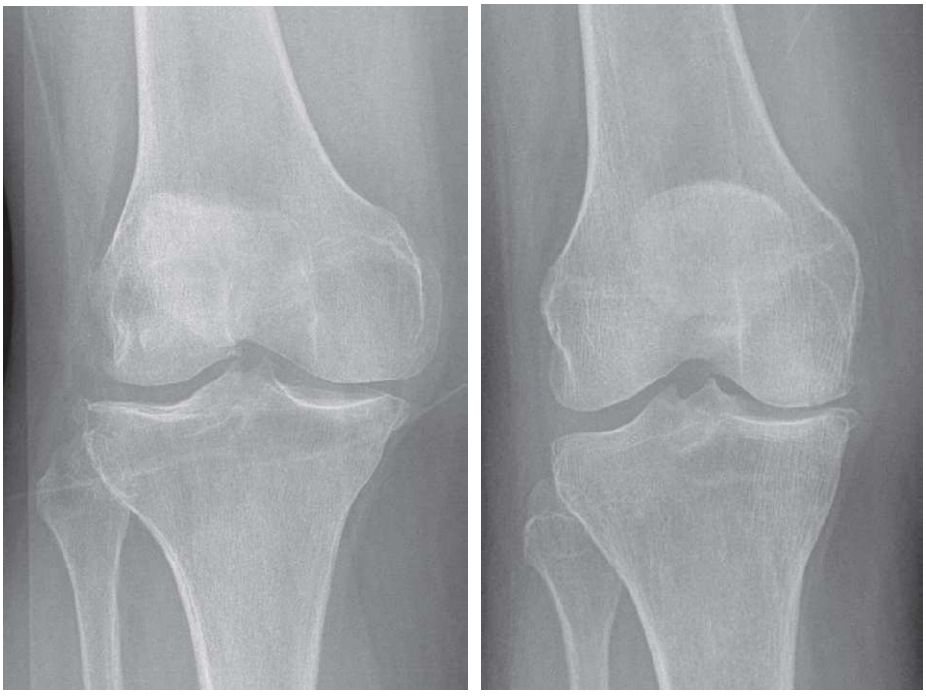
- Lateral, posteroanterior or sunrise views may be necessary.

KELLGREN AND LAWRENCE SYSTEM CLASSIFICATION OF OA KNEE

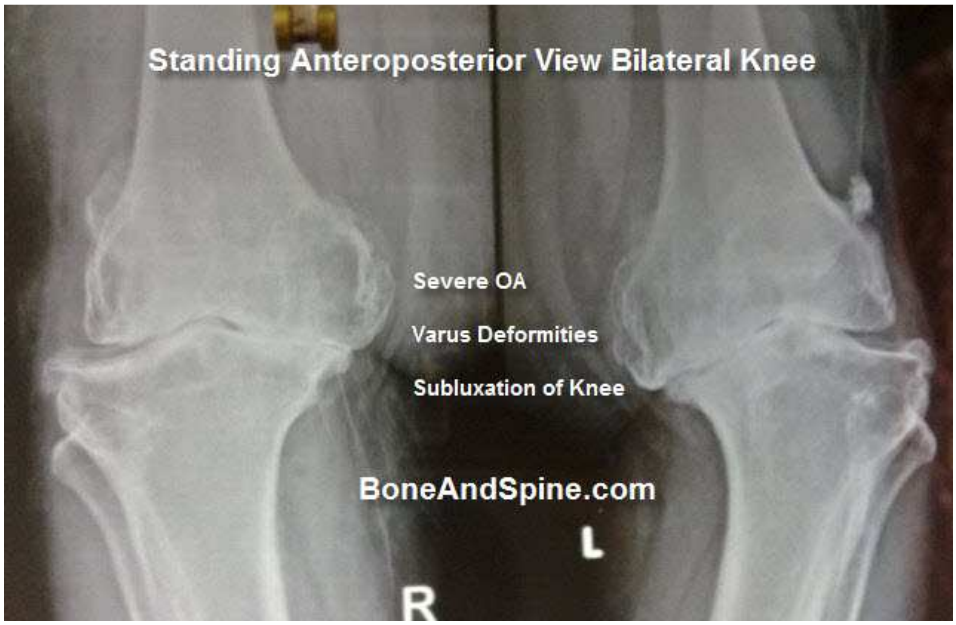
KL system is a method is a classifying the severity of knee OA using five grades:

- **Grade 0 :** no radiographic features of OA present
- **Grade 1 :** doubtful joint space narrowing (JSN) and possible osteophytic lipping.
- **Grade 2 :** definite osteophytes and possible JSN on anteroposterior weight –bearing radiograph
- **Grade 3 :** multiple osteophytes, define JSN, Sclerosis , possible bony deformity
- **Grade 4 :** large osteophytes, marked JSN, severe sclerosis and definitely bony deformity.

KL Grade 2 **KL Grade 3**

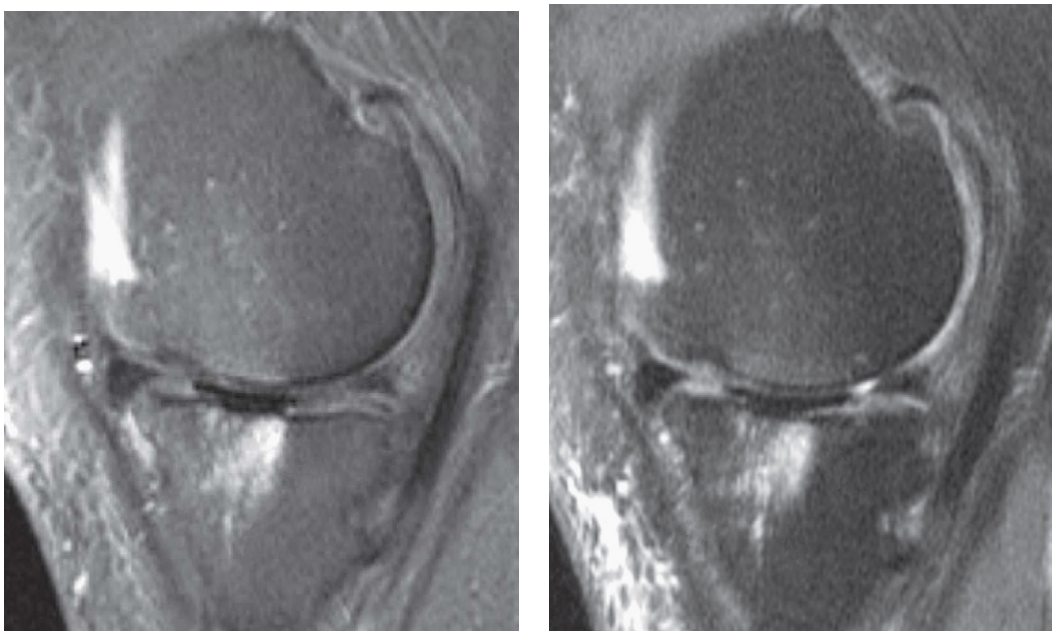


KL Grade 4



ADVANCED IMAGING: (MRI)

- MRI is primarily used for research purpose in OA Knee.
- MRI can be useful in early stages of OA where conventional radiographs findings are inapparent.
- MRI useful in excluding avascular necrosis, stress fractures, occult fractures, infections and inflammatory conditions.
- Bone marrow lesions of knee MRI, correlate with pain, meniscal lesions, bone attrition and progressive cartilage damage.[63,64,65]



Subchondral bone marrow lesions in MRI of OA Knee

USG

USG is being used in detecting small effusion identifying early cartilage changes, differentiates inflammatory and non-inflammatory arthropathies.

USG can be used for accurate aspiration and placement of intra-articular injection[66, 67, 68, 69.]

MORTALITY IN OA

Mortality is increased in OA patient compare to General population.

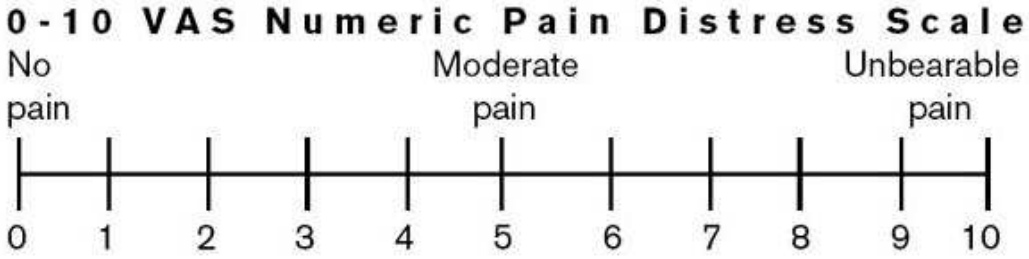
Increasing number of joint involvement causes more mortality.

Co morbid condition and physical inactivity also contribute to increased mortality.

PERFORMANCE MEASURES.

Determination of walking speed time to stand from a chair five times shown to correlate with severity of OA[70,71]

Other functional index (HAQ) Stanford Health Assessment Questionnaire, WOMAC INDEX



WOMAC SCALE

Pain Subscale: (0-20)

How much pain do you have ...

Walking on a flat surface?

Going up or down stairs?

At night while in bed?

Sitting or lying?

Standing upright?

Stiffness Subscale: (0-8)

How severe is your stiffness....

After first waking in the morning?

After sitting, lying down, or resting later in the day?

Function Subscale (0-68)

1. What degree of difficulty do you have with...
2. Descending stairs?
3. Ascending stairs?
4. Rising from sitting?
5. Standing?
6. Bending from floor?
7. Walking on a flat surface?
8. Getting in or out of a car?
9. Going shopping?
10. Putting on socks or stockings?
11. Lying in bed?
12. Getting in and out of the bath?
13. Sitting?
14. Getting on or of the toilet?
15. Heavy domestic duties?
16. Light domestic duties?

For the above symptoms patients are given a likert scale from 0 to 4

TIME TO TOTAL JOINT REPLACEMENT

- Total knee replacement is the “hard end point ” in OA
- Joint replacement is affected by patient decision, procedure availability insurance coverage and co morbid condition.

MANAGEMENT OF OA

- ❖ NON-PHARMACOLOGICAL INTERVENTION
- ❖ Patient education: Patient should understand that nature of OA and it is slowly progressive illness not disabling as inflammatory arthritis.
- ❖ Arthritis self help programmes
- ❖ Weight loss
- ❖ Exercise
- ❖ Orthotics
- ❖ Modified activities of daily living

WEIGHT LOSS

- ❖ Higher body mass index is associated with increased progression of OA knee[72].

- ❖ Valgus and varus deformities associated with obesity worsen the disease symptoms by modulating the effect of weight on knee.
- ❖ Weight loss and exercise leads to improvement in pain and disability in OA of the knee.
- ❖ Reduction in percentage of body fat instead of weight may be significant in reducing pain from OA of the knee[73]
- ❖ Combination of weight loss and exercise is superior either alone[74].

TEMPERATURE MODALITIES

- ❖ Topical application of heat or cold can be help in superficial joints like knee
- ❖ Acute injury responds to cold application whereas chronic pain, most patient prefer warm application
- ❖ Warm applicators-warm soaks or heating pads
- ❖ Individual session should not exceed a temperature of 45.c 0r last more than 30mins[75.]
- ❖ Warmth should not be applied near testicles, and in patients with poor vascular supply, neuropathy or cancer.
- ❖ Benefits of warm applications include decreased pain and stiffness, relief of muscle spasm and prevention of contractures

EXERCISE

- Quadriceps muscle weakness is a risk factor for OA and quadriceps strengthening exercises can be useful in OA.[76,77]
- DYNAMIC AND ISOMETRIC EXERCISE showed equal improvement in symptoms and physical functioning.[78]
- Supervised fitness walking regimens improve function in patients with OA.
- Aquatic exercise programs also have advantage[79]

ORTHOTICS AND BRACINGS

- Lateral wedged insoles provide adequate relief to those with medial compartment knee OA particularly those with varus deformity
- Heel lifts can be useful in patient with hip OA.
- Valgus bracing in patient with medial compartment OA have reduced pain and increased level of activity.[80]

CANE/WALKING AID

- Appropriate use of walking stick (cane) can be useful.
- The cane should be used in hand opposite to the affected knee.
- The appropriate cane size is which produce 20 deg flexion of the elbow during use.

MODIFIED IN ACTIVITIES OF DAILY LIVING

- Avoiding stair cases can reduce pain symptoms and prevent joint damage.
- Switching from high impact activities like jogging or tennis to lower impact activities like swimming or cycling will reduce stress on the knee.
- Elevation of toilet seats or shower bends can be helpful in reducing OA symptoms
- Physicians advice can be extremely helpful in reducing helpful in modifying activities of daily living

OTHER INTERVENTION

- TENS
- ACUPUNCTURE
- SPA therapy
- YOGA
- PULSED ELECTROMAGNETIC FIELDS
- STATIC MAGNETS

PHARMACOLOGIC INTERVENTION

SYMPTOMATIC PHARMACOLOGICAL THERAPIES

Topical
Capsaicin Topical NSAID preparations Topical lidocaine preparations
Systemic
Acetaminophen Nonselective NSAIDs Cyclooxygenase-2–specific inhibitors Tramadol Narcotic analgesics
Intra-articular
Corticosteroids Hyaluronic acid derivatives

NSAID, nonsteroidal anti-inflammatory drug.

TOPICAL AGENTS

- Capsaicin, mechanism of action through selective stimulation of unmyelinated type C afferent neurons, causing the release of substance P.
- This release reversibly depletes the stores substance P, where is a neurotransmitter of peripheral pain sensation.[81]
- Topical NSAIDS preparation include diclofenac and elfenac have been found useful
- Transdermal lidocaine 5% patches are available for management of pain.

SYSTEMIC AGENTS

NON-NARCOTIC ANALGESICS

- Acetaminophen (paracetomol) can be used for pain relief at the initial systemic treatment.
- Acetaminophen may have effect in relieving pain, results are inferior to NSAIDS does not have effect on stiffness and functional score .
- It does not have anti inflammatory effects at approved doses.[82]
- Simultaneous use of alcohol can lead to liver disease at therapeutic levels.

NSAIDS

- NSAIDS act through non specific inhibition of cyclo oxygenase isoforms 1 and 2.COX-1 expressed in renal and gastrointestinal tissues.
- Major adverse effects of NSAIDS are GI toxicities (gastritis, peptic ulcer disease) and renal toxicities i.e., interstitial nephritis, prostaglandins inhibition related renal insufficiency.
- Rofecoxib was withdrawn due to cardiac risks.
- All NSAIDS and COX-2 inhibitors received black box warning due to CVS risk.

- ❖ Now selective NSAIDS are ibuprofen, naproxen and diclofenac.
- ❖ NSAIDS are analgesic at lower doses but have both analgesic and anti-inflammatory effects at higher doses.
- ❖ PPI prostaglandin E2 analogue misoprostol can reduce GI adverse effects.

NARCOTIC ANALGESICS

- ❖ Narcotics should be considered if patient failed to respond to other non-pharmacologic and pharmacologic measures
- ❖ Tramadol has suppressive effects of mu receptors used in symptom relief of OA.
- ❖ Transdermal fentanyl used in the treatment of moderate to severe OA knee patients.

INTRA ARTICULAR AGENTS

- ❖ Corticosteroids down regulate expression of cell adhesion molecules.
- ❖ Corticosteroids injection causes decrease in cell infiltration of the synovium.
- ❖ Dose of steroids depends upon the volume of joint involved.
- ❖ Intraarticular injection has short term benefits but long term benefits have been not confirmed.[83]

- ❖ In general steroids injections are found to be most effective in patient with evidence of inflammation, effusion or both.
- ❖ No more than 4 injections per year are given to particular joint.

HYALURONIC ACID DERIVATIVES

- ❖ Synthetic and natural HA derivative can be administrated intra articularly.
- ❖ They reduce pain for prolonged periods and improve joint mobility.[84]
- ❖ Mechanisms of action include lubricant effect in short term analgesic effect and stimulating effect of synovial lining cells, producing normal HA.
- ❖ Greater improvement in pain, decrease in joint space narrowing have been demonstrated.

NUTRACEUTICALS

GLUCOSAMINE

- Urinary glucosamine found to be elevated in both OA and rheumatoid arthritis.
- Supplementation with glucosamine sulfate has been tried orally and intramuscularly.
- Cochrane review of glucosamine therapy analysed 20 studies and 2570 patients, pain and function improved by 28% and 21% respectively.
- Combination products glucosamine and chondroitin sulfate have been studied found to be more efficacious in more severe symptomatic patients.

CHONDROITIN SULFATE

- Chondroitin sulfate has been used as therapy for hip and knee OA.
- Mechanism of action unknown
- One study showed decreased use of NSAIDS.
- One study evaluated chondroitin sulfate 300 pts enrolled and randomized trial to chondroitin sulfate 800mg daily for two years, decreased joint space narrowing and functional improvement was found in study group.

OTHER NUTRACEUTICALS

- Glucosamine
- Chondroitin sulfate
- Ginger extracts
- Avocado and soy unsaponifiables
- Cat's claw
- Shark cartilage
- S-adenosyl methionine

1) GINGER EXTRACTS: Contains small amount of salicylates.[85] Ginger has inhibitory effects on COX and lipoxygenase

2) Avocado and soy unsaponifiable residue contains oils in ratio 1: 2; ASU has inhibitory effects of IL-1β and decreased production of IL-6, IL-8 and MMPS

3) S-adenosyl methionine has tried for OA remedy, but evidence is insufficient to recommend its use.

POTENTIAL STRUCTURE AND DISEASE MODIFYING DRUGS IN OA

- Tetracyclines
- Metalloproteinase or collagenase inhibitors
- Glucosamine
- Diacerin
- Growth factors and cytokine IL-1 Receptor antagonist
- Chondrocyte and stem cell transplantation

NEW APPROACH FOR OSTEOARTHRITIS

PLATELET RICH PLASMA INJECTION:

Platelets and plasma portion of blood contain factors that are useful for cell recruitment, multiplication and specialisation that are required for healing.

PRP is obtained from patient own blood where the blood sample is centrifuged and platelet rich plasma is separated which is injected into affected joint with ultrasound guidance.

Patient after PRP injection should avoid exercise for a short period of time then he can start a rehabilitation exercise program.

In one prospective study of 22 patients, there was important in pain as with improvement in WOMAC pain scores and improvement in joint stiffness.

In one small study PRP treatment was shown to be more effective than hyaluronic acid treatment.

OTHER USES OF PRP:

- Lateral epicondylitis –Tennis Elbow.
- Achilles tendon injuries
- Rotator cuff tears.
- Medial collateral ligament injuries.

SURGICAL INTERVENTION

Osteotomies are effective pain relieving intervention and can delay need for joint replacement surgery in some patient particularly young patients.

- **Joint replacement** surgery has provided pain relief and restoring function.

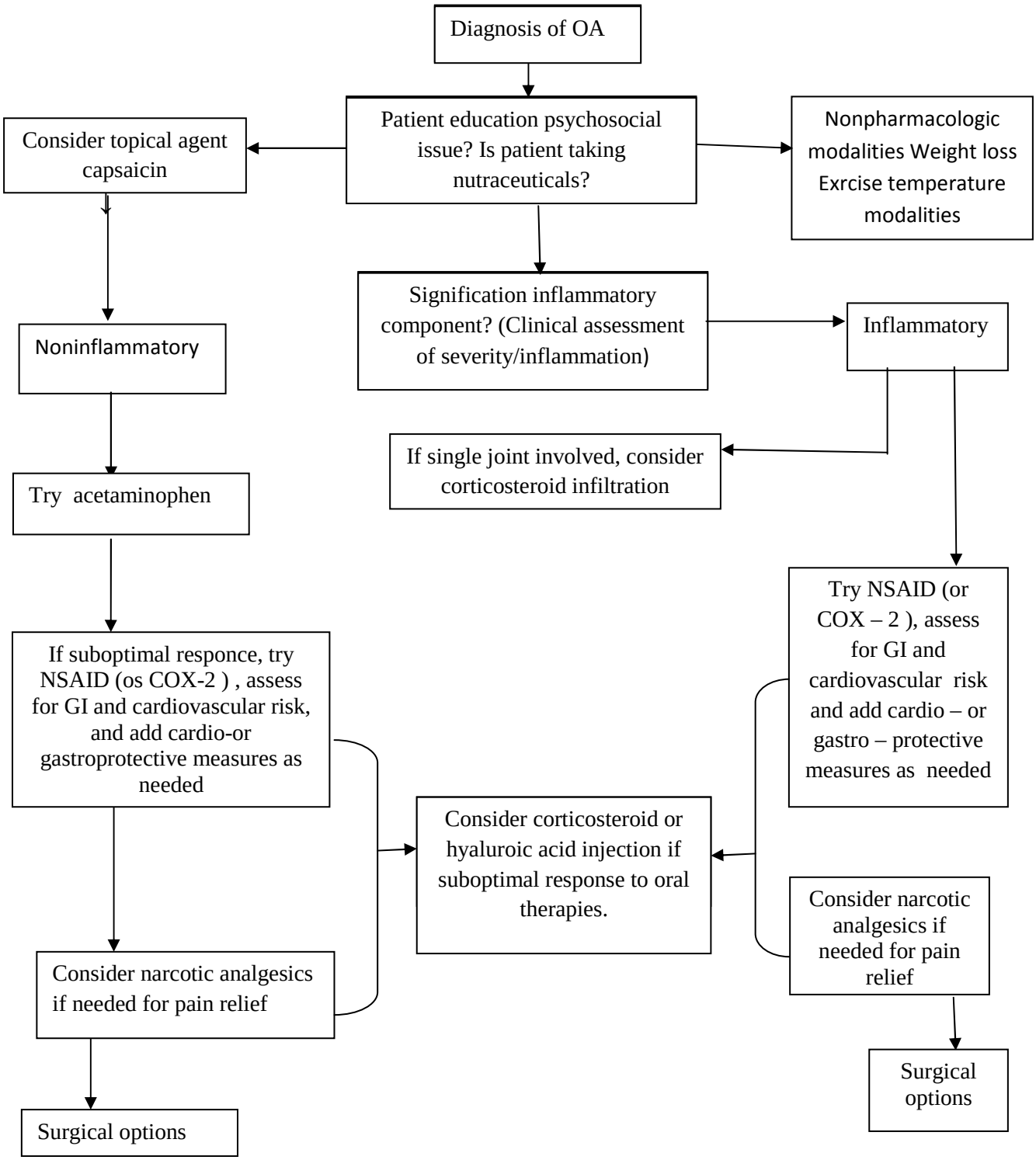
- Indications for surgery include pain refractory to medical management and other measures along with serious impairment of patient daily life.

- Infections are rare but do occur.

- Joint replacement has life span of 10-15 years revision surgery may be necessary.

- Loose body removal and stabilisation of joints are other indication for surgery.

ALGORITHM FOR THE MANAGEMENT OF OSTEOARTHRITIS



Elevated High Sensitivity C-Reactivity Protein in Osteoarthritis

- C- reactive protein (CRP) commonly used to differentiate systemic inflammatory disorder i.e., rheumatoid arthritis from OA.
- With recent development of high sensitivity CRP assays, CRP levels lower than traditional assays can be detected.
- If there is inflammatory component hsCRP can be elevated modestly.
- In rheumatoid arthritis hsCRP level is more than 15 mg/L, but in OA it ranges from 3 to 8 mg/L, which is more than the normal population.
- Measuring hsCRP in OA patients may be helpful in detecting patient with local inflammation.
- It has been found that elevation in hsCRP can lead to radiographic progression.
- Elevation in hsCRP may also correlate with clinical severity.

OTHER CAUSES OF hsCRP ELEVATION

- Recurrent coronary events.
- COPD.
- Rheumatoid arthritis.
- Asthma.
- SLE.
- Diabetes mellitus.
- Smoking.

MATERIALS

AND

METHODS

MATERIALS AND METHODS

SELECTION OF VOLUNTEERS:

On patient found to have clinical evidence of osteoarthritis of knee are selected and subjected to cross sectional study. They are subjected to detailed history, clinical examination, and radiographic evaluation of knee along with high sensitive C - reactive protein. Then it is planned to assess the correlation if any exist between clinical symptoms, radiological findings and hsCRP levels.

STUDY CENTRE:

Department of Rheumatology, Madras Medical College and Rajiv Gandhi government General Hospital, Chennai.

DURATION OF THE STUDY

6 Months

STUDY DESIGN

Observational study

SAMPLE SIZE

60 patients

DATA COLLECTION AND METHODS

Patients have their history taken according to a questionnaire and subjected to clinical examination and investigations.

PRODUCT / PROCEDURE / INVESTIGATION DETAILS

X-ray knee, hsCRP levels.

INCLUSION CRITERIA

- Idiopathic osteoarthritis
- Patient with evidence of clinical osteoarthritis
- Patient aged 40 Yrs and above.

EXCLUSION CRITERIA

- Patients with inflammatory rheumatologic disorders RA, SLE, crystal arthropathies, Reactive arthritis.
- Cardiovascular disease,
- COPD,
- Ulcerative colitis.
- Chronic liver, Kidney Diseases,
- Previous history of local intraarticular steroid injection.

STATISTICAL METHODS

The statistical analysis is done

SPONSORSHIP

No

CONFLICT OF INTEREST

None.

OBSERVATION

AND

RESULTS

OBSERVATION AND RESULTS

In our study 60 patients found to have osteoarthritis of knee were enrolled as participants. Osteoarthritis patients are diagnosed by history and clinical examination. Our study was conducted between April 2015 and September 2015. Aims of the study and study design were explained and institutional ethics clearance obtained.

Osteoarthritis patient enrolled and the purpose of study explained to the participants. After the informed consent of the participants detailed history and clinical examination were done. Patients who were satisfying ACR criteria for osteoarthritis of knee were considered for study. Patients with evidence of inflammatory arthritis were excluded, so also there with secondary mellitus, hypertensions, chronic liver disease, chronic kidney disease were excluded from the study because these factors may interfere with our study outcome.

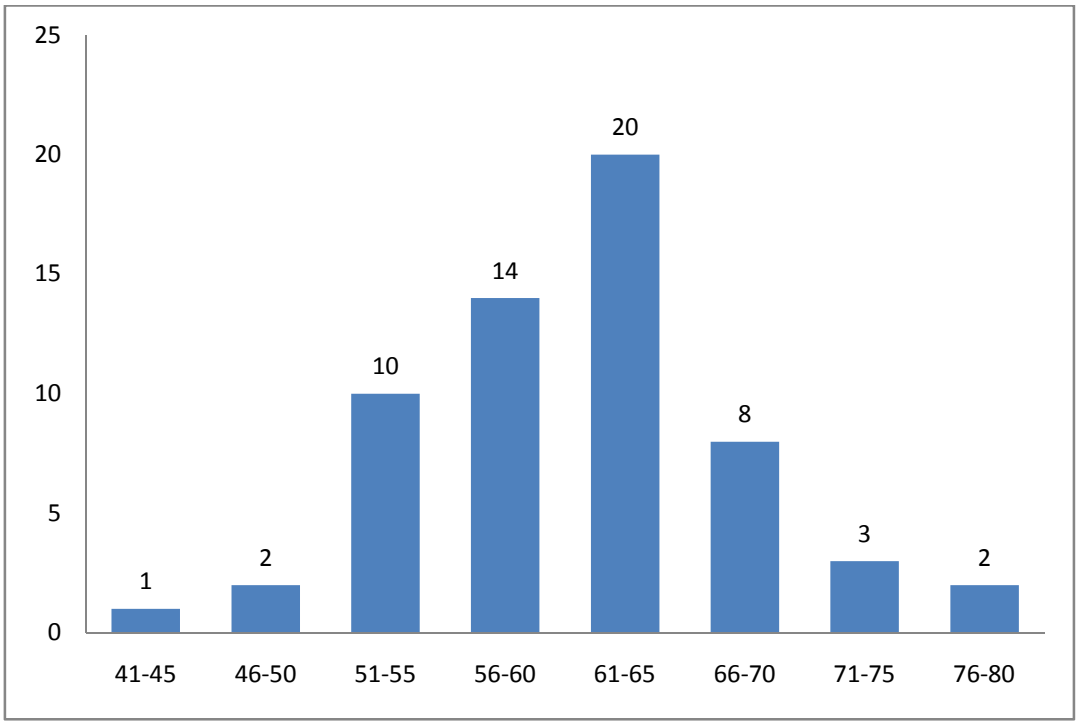
Symptoms of the patients such as pain, stiffness, swelling and disability were enquired. Pain was graded by visual analog scale (VAS) graded from 0 to 10 cm. (No pain on the left side of scale to extreme pain on right).

All the patients were examined clinically and their body mass index calculated, examined for effusion and tenderness and joint deformity.

X-Ray of both knee joints taken in standing posture, grading of X-Ray changes done by Kellgren and Lawrence system which is from 0 to changes done by Kellgren and Lawrence system which is from 0 to 4. All our patients were more than K-L grade 2.

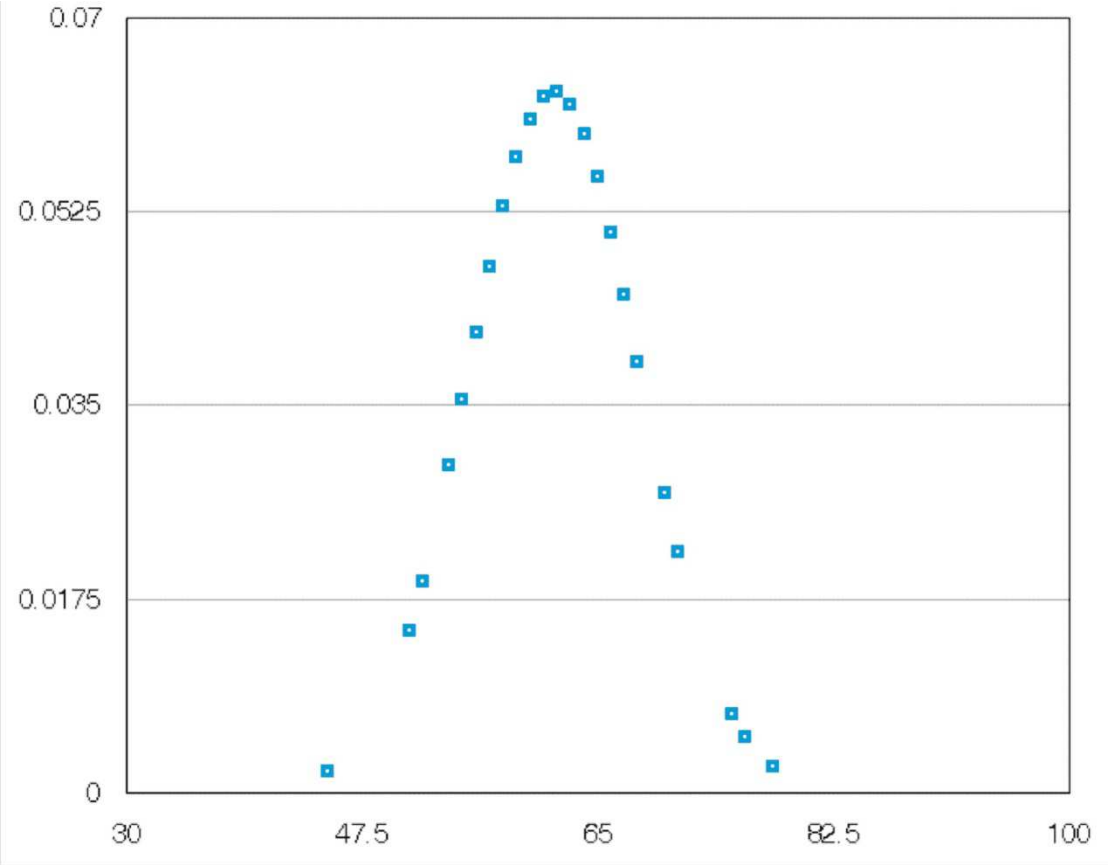
Blood sample 5ml collected from each patient and centrifuged to collect the plasma and stored in frozen state. After collecting all samples hsCRP levels estimated by ELISA technique after making adequate dilution.

AGE DISTRIBUTION CHART



(Standard deviation 6.31mean 61.45)

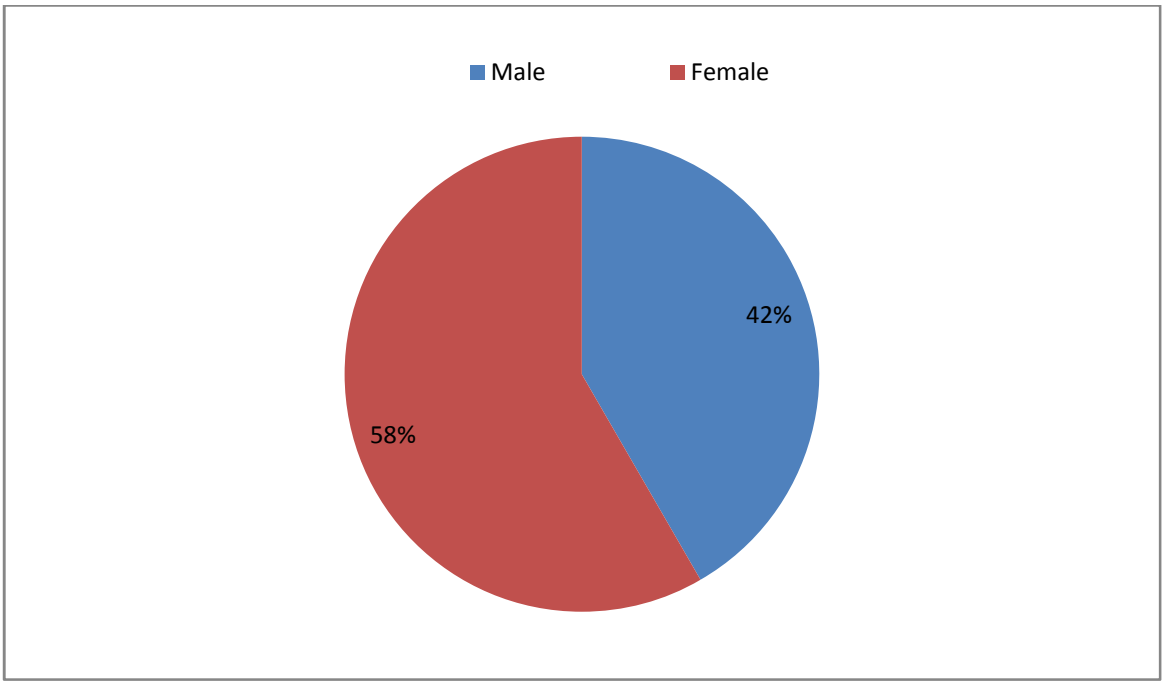
STANDARD AGE DISTRIBUTION IN OUR PATIENT



Age group	Total	Percentage
41-45	1	1.6
46-50	2	3.3
51-55	10	16.7
56-60	14	23.3
61-65	20	33.4
66-70	8	13.4
71-75	3	5
76-80	2	3.3

1. From our study age distribution chart shows as age advances prevalence of osteoarthritis increases.
2. Mean age of our study group is 61.45 yrs, with minimum 45 yrs and max 78 yrs.
3. Standard deviation of 6.31.
4. Maximum incidence was in the age group 61-65 yrs.
5. Irrespective of age group females are affected more than males.

SEX DISTRIBUTION



1. Out of 60 patients studied 25 are male and 35 are female.
2. There is more prevalence of osteoarthritis in female patients in our study.

BMI DISTRIBUTION

Gender	Number	Percentage
Male	25	42
Female	35	58

In our study BMI ranges from 18.49 to 29.43 around 73.36% of our patient are the category of overweight and obesity.

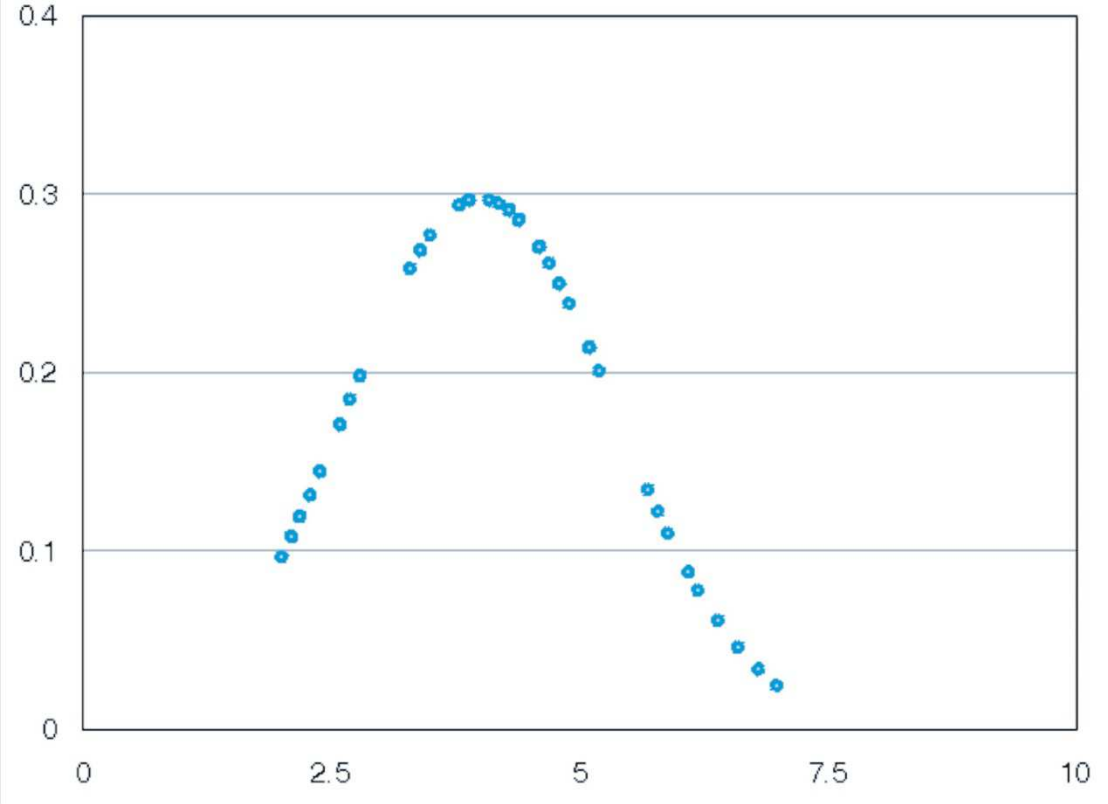
Average BMI of males in our group is 23.97,

Average BMI of females in our group is 24.40.

In our study none of the patient had BMI more than 30.

Standard Distribution of hsCRP in our patient

- Mean hsCRP level in our patient 4.0 mg/dl
- hsCRP level in our patient ranges from 2.0mg/dl to 7.0 mg/dl,
- hsCRP is more than that of healthy general population. (>1.1 mg/dl)



PAIN DISTRIBUTION IN OUR PATIENT

Pain Score	No. Of Patient
VAS 3	3
VAS 4	10
VAS 5	7
VAS 6	26
VAS 7	14
VAS 8	0

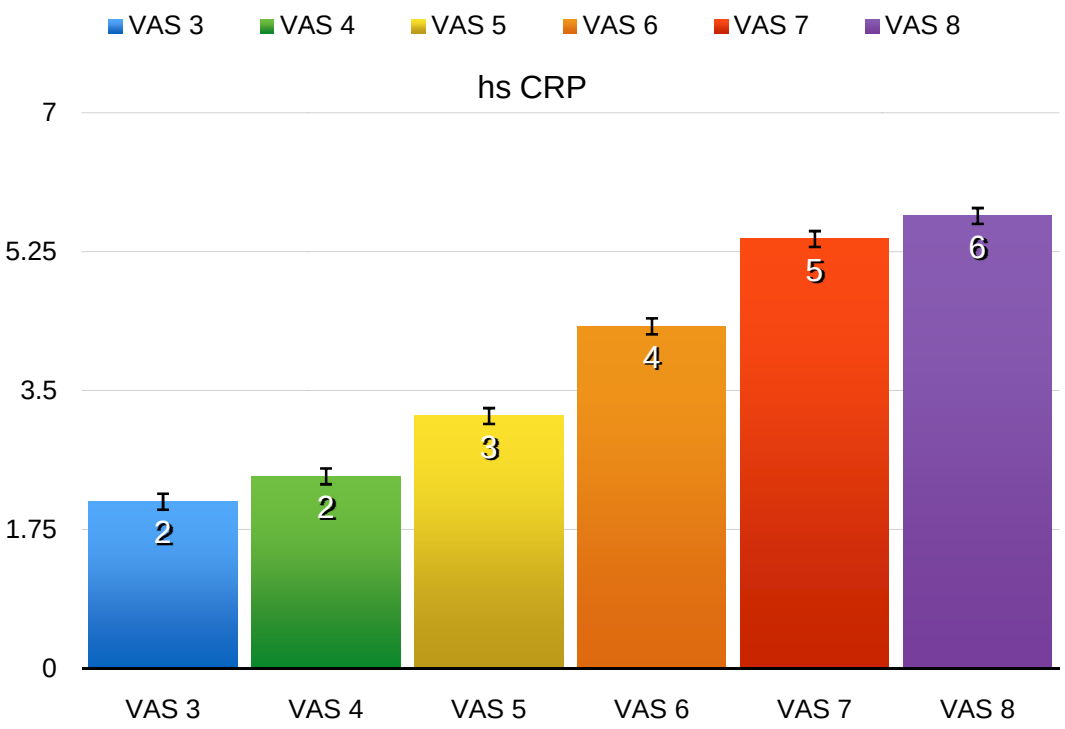
- Most of our patient symptomatic with pain range from mild moderate and sever.
- Average pain score of our patient is 5.6 in VAS Scale.

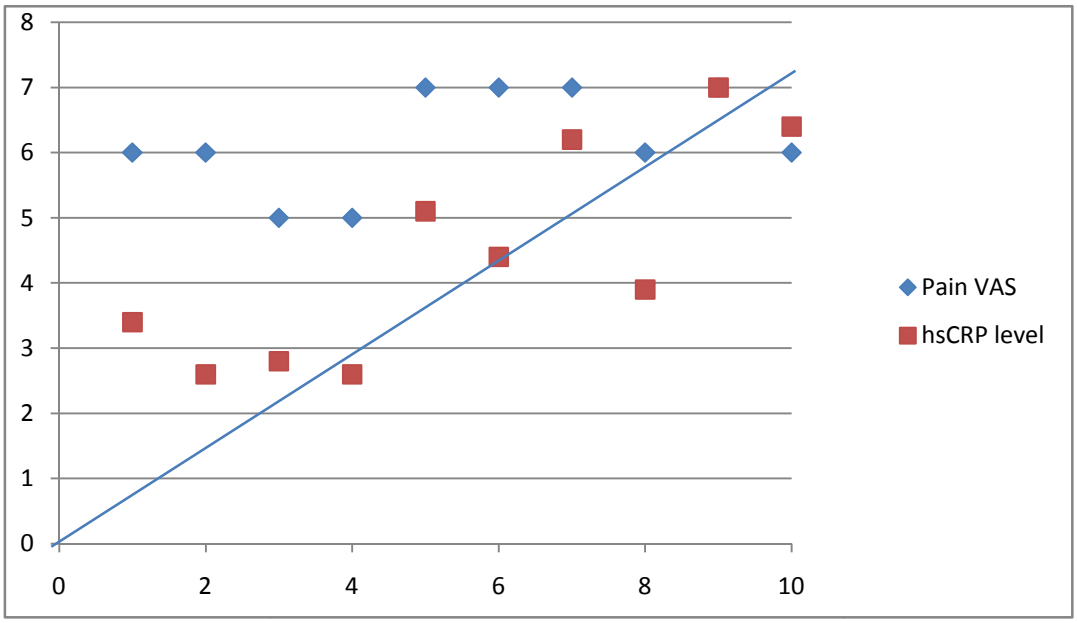
X-ray – KL grading distribution

X RAY GRADE KL	No. Of patients
GRADE 2	20
GRADE 3	26
GRADE 4	14

- Many of our patients belong to grade 3KL Grading.
- Pain severity does not match with KL Grading.
- Deformity is present in Grade 3 and Grade 4 patient.

ANALYSIS OF hsCRP LEVELS AND PAIN SCALE



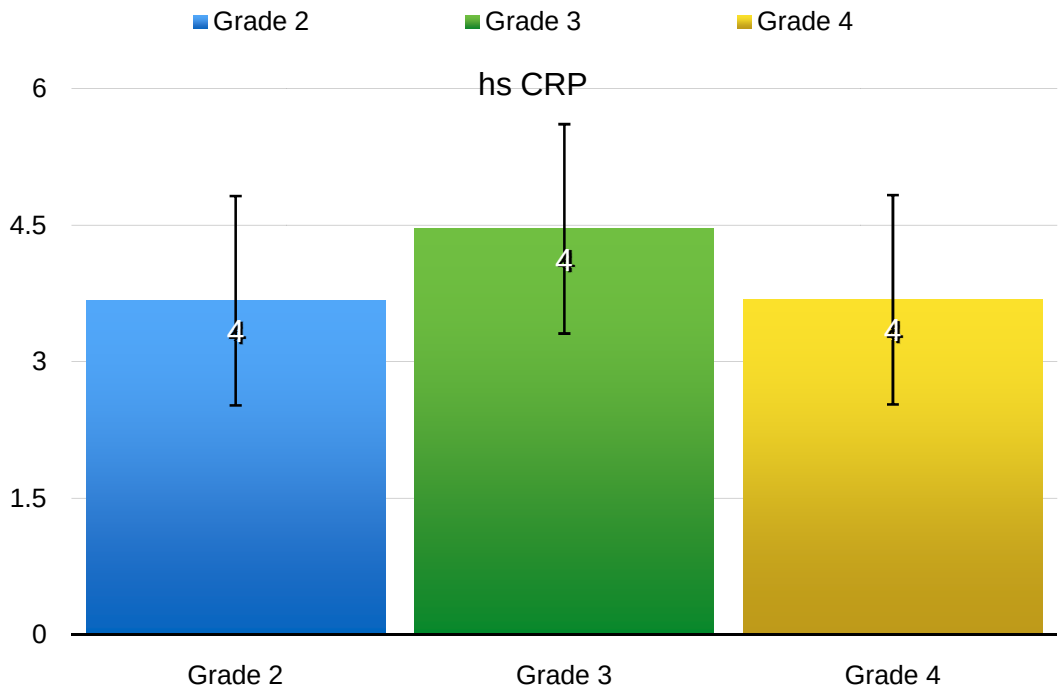


SCATTER GRAPH BETWEEN PAIN (VAS) AND hsCRP

Data Summary						
	Samples					
	VAS 3	**VAS 4**	**VAS 5**	**VAS 6**	**VAS 7**	**Total**
N	3	10	7	26	14	60
ΣX	6.3	24.2	22.3	112.1	76.1	241
Mean	2.1	2.42	3.1857	4.3115	5.4357	4.0167
ΣX^2	13.25	59.92	75.41	498.89	428.79	1076.26
Variance	0.01	0.1507	0.7281	0.6227	1.164	1.8346
Std. Dev.	0.1	0.3882	0.8533	0.7891	1.0789	1.3545
Std. Err.	0.0577	0.1227	0.3225	0.1548	0.2883	0.1749

X = hsCRP

Standard weighted – means analysis					
ANOVA Summary Independent Samples k=5					
Source	**SS**	**df**	**MS**	**F**	**P**
Treatment [between groups]	71.8001	4	17.95	27.09	**<.0001**
Error	36.4433	55	0.6626		
Ss/BI					
Total	108.2434	59			

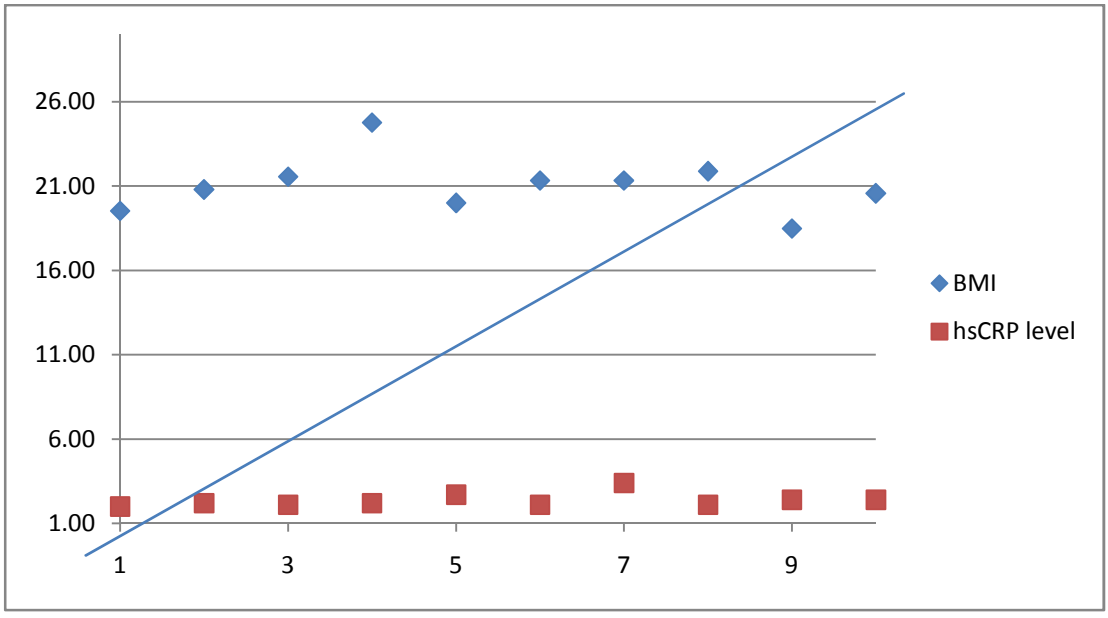


ANALYSIS OF hsCRP AND KL GRADING

Data Summary				
	Samples			
	KL Grade 2	KL Grade 3	KL Grade 4	Total
N	20	26	14	60
ΣX	73.5	115.9	51.6	241
Mean	3.675	4.4577	3.6857	4.0167
ΣX^2	295.39	555.61	225.26	1076.26
Variance	1.3304	1.5585	2.6982	1.8346
Std. Dev.	1.1534	1.2484	1.6426	1.3545
Std. Err.	0.2579	0.2448	0.439	0.1749

Standard weighted- means analysis					
ANOVA SUMMARY Independent Samples k=3					
Source	**SS**	**Df**	**MS**	**F**	**P**
Treatment [between groups]	8.9252	2	4.4626	2.56	**0.086166**
Error	99.3181	57	1.7424		
Ss/BIs					
Total	108.2433	59			

ANALYSIS OF BMI AND hsCRP



PEARSONS CORRELATION METHOD

Result Details & calculation	**Key**
X values $\Sigma = 1453.19$ Mean = 24.22 $\Sigma(X-M_x)^2 = SS_x = 478.253$ Y values $\Sigma = 241$ Mean = 4.017 $\Sigma(Y - M_y)^2 = ss_y = 108.243$ X and Y combined N = 60 $\Sigma(X-M_x)Y-M_y) = 156.146$ R Calculation $r = \Sigma((X-M_y)(Y-M_x)) / \sqrt{((SS_x)(SS_y))}$ $r = 156.146 / \sqrt{((478.253)(108.243))} = 0.6863$ Meta Numerics (cross-check) r = 0.6863	X: BMI Values Y : hsCRP Values M_x: Mean of BMI Values M_y: Mean of hsCRP Values $X - M_x$ & $Y - M_y$: Deviation Scores $(X - M_x)^2$ & $(Y - M_y)^2$: Deviation Squared $(X - M_x)(Y - M_y)$: Product of Deviation scores

The value of R is 0.6863. This is a moderate positive correlation, which means there is a tendency for high X (BMI) variable scores go with high Y (hsCRP) variable scores (and vice versa).

DISCUSSION

DISCUSSION

- When compared to study by A.D pearle, C.R.Scanzello et al. our patient had similar sex distribution with increased female prevalence
- Mean age in our patient was 61.45 years compared to 64.2 years, by A.D pearle, C.R.Scanzello et al.
- Mean BMI in our study 24.22 compared to 28.50 in their study showing that our patient had osteoarthritis with lower BMI levels.
- K.L.grade severity is comparable to that of study by A.D pearle, C.R.Scanzello et al. median K.L grade 3.
- Mean hsCRP levels 4.0 mg/dl in our study compared to 2.4 mg/dl studied by T.Sturmer, H.Brunner et al.
- Comparing hsCRP and pain scales both our study by T.Sturmer, H.Brunner et al. showed statistically significant association between hsCRP and pain symptoms.
- Comparing hsCRP and K.L grading our study had no statistically significant correlation with hsCRP levels as studied by T.Sturmer, H.Brunner et al.
- BMI had mild correlation with hsCRP levels as compared to study by A.D.Pearle et al.

CONCLUSION

CONCLUSION

In our studyof hscrp levels in osteoarthritis patients the following conclusions are

- Osteoarthritis is more prevalent in females.
- hscrp levels are modestly elevated in many patients particularly those with local symptoms .
- hscrp levels rise with increasing pain scores.
- hscrp levels do not correlate with x-ray grading .
- hscrp levels have minimal correlation with body mass index.
- patients with high levels of hscrp are likely to progress to advance disease.

LIMITATIONS

LIMITATION OF STUDY

- Our study size is small for comarision of for the large population.
- Extrems of BMI were not taken into account.
- Our patients are symtamatic hence hsCRP levels in A-symptomatic patient or not included in our study.
- Our study did not have controles subject, hsCRP control level is taken general population.

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ANNEXURES

ABBREVIATIONS

HsCRP	-	high sensitive Creactive protein
K-L GRADE	-	Kellgren and Lawrence Grading
I-L	-	Interleukin
ACR	-	American College of Rheumatology
COMP	-	Cartilage Oligomeric Matrix Protein
VAS	-	Visual Analog Scale
OARSI	-	Osteoarthritis Association Research Society International
BMI	-	Body Mass Index
MMP	-	Matrix MetalloProteinase
CPPD	-	Calcium PyroPhosphate Dehydarate
HA	-	Hyaluronic Acid
CTX-II	-	C-Terminal telopeptide of type 2 collagen
WOMAC	-	Western Ontario MacMaster Arthritis Index
COX	-	Cyclo-oxygenase
NSAIDS	-	Nonsteroidal Anti-inflammatory drugs
UA	-	Uric ACID

PROFORMA

Name :

Age/Sex : Weight :

IP No : Height :

Patient ID No : Diagnosis :

Duration :

Patient characteristics	**Medications**	
❑ Smoking	❑ NSAIDS	
❑ Alcoholism	❑ Statins	
❑ Diabetes		
❑ Systemic hypertension	❑ Others	
❑ Coronary events		

Symptoms	
❑ Pain	
❑ Stiffness	
❑ Physical function	
❑ Restriction of activities of daily living	

Clinical examination			
BMI	Knee		
	Effusion		
	Warmth		

	Deformity		
	Crepitus		
	Range of movements		
	Joint line tenderness		
	Synovial thickening		

Serum hsCRP level

<3	**3-8**	**>8**

INFORMATION SHEET

We are conducting a study on **"STUDY OF hsCRP LEVEL IN OSTEOARTHRITIS KNEE WITH CLINICAL AND RADIOLOGICAL CORRELATION"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to show the relationship of hsCRP in Osteoarthritis patients with clinical symptoms and radiological signs.

We are selecting certain cases and if you are found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator | Signature of Participant

Date :
Place :

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனையில் ஆஸ்டியோ ஆர்த்தைடிஸ் எனும் முடக்குவாதம் பற்றி ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது.

இந்த நோயினால் பாதிக்கப்பட்டவர்களை பரிசோதனை செய்து அவர்களின் இரத்தத்தில் hsCRP அளவை கண்டறிந்து, மூட்டு கதிர்வீச்சு (X-ray) மாற்றங்கள் மூலம் நோயின் தாக்கத்தை ஒப்பிட்டு அறிய முயற்சிப்பதே இந்த ஆராய்ச்சியின் நோக்கமாகும். இதற்காக 3 மி.லி. இரத்தம் எடுத்து பரிசோதனை செய்யப்படும். எலும்பு மூட்டு எக்ஸ்ரே எடுக்கப்படும். இந்த பரிசோதனைகள் இலவசமாக செய்யப்படுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆய்வின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறேம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

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ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

PATIENT CONSENT FORM

Study Detail	:	**STUDY OF hsCRP LEVEL IN OSTEOARTHRITIS WITH CLINICAL AND RADIOLOGICAL CORRELATION**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☐) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression
Patient's Name and Address:

Signature of Investigator
Study Investigator's Name:
Dr. S. SENTHIL KUMAR

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு :

ஆஸ்டியோ ஆர்த்ரைடிஸ் முடக்குவாதம் எனும் நோயினால் பாதிக்கப்பட்டவர்களின் இரத்தத்தில் எச்.எஸ்.சி.ஆர்.பி (hsCRP) அளவை கண்டறிந்து நோயின் தாக்கத்தை கண்டறிதல்

பெயர் :	தேதி :
வயது :	வெளி - உள்நோயாளி எண் :
பாலினம் :	ஆராய்ச்சி சேர்க்கை எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டன. எனக்கு விளக்கப்பட்ட தகவல்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

ஆஸ்டியோ ஆர்த்ரைடிஸ் (முடக்குவாதம்) எனும் நோயினில் எச்.எஸ்.சி.ஆர்.பி (hsCRP)-ன் பங்களிப்பை கண்டறிய மேற்கொள்ளப்படும் பரிசோதனைகளைப் பற்றி ஆராய்ச்சியாளர் கூற முழுவதும் விளங்கப்பெற்றேன்.

மேற்கொண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம்

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.S.Senthil Kumar
Postgradaute M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.S.Senthil Kumar,

The Institutional Ethics Committee has considered your request and approved your study titled **"Study of hsCRP levels in Osteoarthritis knee with clinical and radiological correlation" No.08052015.**

The following members of Ethics Committee were present in the meeting held on 12.05.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
7. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
8. Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
9. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

30/6/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI

MASTER CHART

MASTER CHART

S.No	Age	Sex	Height	Weight	BMI	Pain VAS	Swelling	Deformity	KL Grade	hsCRP level
1	62	F	150	50	22.22	6	YES	No	3	3.4
2	55	M	170	62	21.45	7	YES	No	3	3.9
3	54	F	154	60	25.3	6	No	No	2	2.6
4	60	M	160	58	22.66	7	No	No	3	3.5
5	65	F	152	52	22.51	5	No	Yes	3	2.8
6	54	M	160	62	24.22	6	YES	No	2	4.3
7	52	F	152	45	19.48	5	No	No	2	2.6
8	58	M	170	65	22.49	6	YES	No	2	3.3
9	75	F	160	55	21.48	7	YES	Yes	3	5.1
10	65	M	167	65	23.31	7	YES	No	3	4.6
11	67	F	156	55	22.6	7	YES	No	2	4.4
12	59	M	168	66	23.38	6	YES	No	3	4.8
13	65	F	155	65	27.06	7	YES	No	3	6.2
14	56	M	160	65	25.39	6	No	No	2	4.6
15	54	F	154	60	25.3	6	No	No	2	3.9
16	60	M	160	67	26.17	4	No	Yes	3	2.4
17	57	M	165	62	22.77	6	YES	No	2	3.3
18	65	M	160	70	27.34	7	YES	No	2	6.8
19	66	F	155	65	27.06	7	YES	Yes	4	7
20	51	M	162	59	22.48	4	No	No	2	2.2
21	49	F	158	68	27.24	6	YES	Yes	3	6.4
22	78	M	160	70	27.34	6	YES	Yes	4	5.8
23	60	F	155	66	27.47	6	YES	No	3	5.1
24	76	M	164	58	21.56	3	No	Yes	4	2.1
25	60	F	146	52	24.39	5	YES	No	3	4.4
26	61	M	163	54	20.32	6	YES	No	2	4.6
27	63	F	152	60	25.97	6	YES	No	2	4.1
28	62	M	163	60	22.58	5	No	No	2	2.8
29	63	F	160	64	25	6	No	No	3	3.8
30	54	M	160	65	25.39	5	No	No	2	3.4

MASTER CHART -2

S.No	Age	Sex	Height	Weight	BMI	Pain VAS	Swelling	Deformity	KL Grade	hsCRP level
31	58	F	150	60	26.67	6	YES	No	2	4.6
32	62	M	163	60	22.58	6	YES	Yes	4	3.8
33	63	F	162	65	24.77	4	No	Yes	4	2.2
34	66	M	160	75	29.30	6	YES	Yes	4	4.3
35	65	F	150	56	24.89	6	YES	No	2	4.6
36	65	M	158	69	27.64	7	YES	No	3	5.2
37	57	F	160	70	27.34	6	YES	Yes	3	4.8
38	70	M	162	73	27.82	7	YES	Yes	4	5.7
39	62	F	152	68	29.43	7	YES	Yes	3	5.9
40	56	M	165	56	20.57	5	No	No	2	2.1
41	55	F	150	65	28.89	6	YES	No	3	4.9
42	70	M	168	62	21.97	4	No	Yes	4	2.3
43	56	F	158	68	27.24	5	YES	No	2	4.2
44	45	F	150	45	20.00	4	No	No	2	2.7
45	56	F	155	65	27.06	6	YES	No	3	3.9
46	64	F	160	50	19.53	3	No	Yes	4	2
47	64	F	150	48	21.33	4	No	No	3	2.1
48	65	F	150	65	28.89	6	YES	Yes	4	4.3
49	71	F	150	48	21.33	4	No	Yes	4	3.4
50	65	F	156	69	28.35	7	YES	No	3	6.1
51	47	M	168	64	22.68	6	YES	No	3	3.9
52	58	F	150	55	24.44	6	YES	No	3	4.7
53	67	F	156	60	24.65	7	YES	No	3	5.1
54	71	F	160	56	21.88	4	YES	Yes	4	2.1
55	54	F	156	45	18.49	4	No	No	2	2.4
56	68	M	165	59	21.67	6	YES	No	3	3.9
57	63	F	160	62	24.22	6	YES	Yes	4	4.4
58	55	F	165	56	20.57	4	No	No	3	2.4
59	65	F	167	58	20.80	3	No	Yes	4	2.2
60	66	M	169	75	26.26	7	YES	Yes	3	6.6

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INTRODUCTION

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